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(54) Sulfonylaminocarbonyl derivatives for the treatment of nuclear factor-kappa B mediated diseases and disorders

(57) The present invention provides a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof. The methods of the present invention are useful for treating, for example, rheumatoid arthritis, osteoarthritis, an autoimmune disease, psoriasis, asthma, a cardiovascular disease, an acute coronary syndrome, congestive heart failure, Alzheimer's disease, multiple sclerosis, cancer, type II diabetes, metabolic syndrome X, or inflammatory bowel disease.

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Description

FIELD OF THE INVENTION

[0001] The present invention provides methods of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to patients in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof.

BACKGROUND OF THE INVENTION

[0002] Inhibition of nuclear factor-kappa B ("NF-κB") transcription factor-mediated activity would provide valuable methods of treating a disease or a disorder afflicting millions of people worldwide. This is so because NF-κB mediates transcription of a large number of genes involved in the production of pro-inflammatory cytokines and other biomolecules intimately involved in the etiology of many diseases and disorders for which no completely effective treatment is available. Noteworthy among the diseases and disorders thought to be responsive to the inhibition of NF-κB are rheumatoid arthritis and osteoarthritis, autoimmune diseases, psoriasis, asthma, cardiovascular diseases such as, for example, atherosclerosis, acute coronary syndromes including myocardial infarction and unstable angina, and congestive heart failure, Alzheimer's disease, multiple sclerosis, cancer, type II diabetes, metabolic syndrome X, and inflammatory bowel disease ("IBD"). These diseases and disorders are among the most prevalent in society today and cause untold suffering and death.

[0003] Current methods of treatment of the above mentioned diseases and disorders are unsatisfactory, as they typically require surgical alteration or removal of the affected body part or the use of pharmaceuticals that treat symptoms, without stopping or, ideally, reversing the underlying disease process. For example, while there are many marketed agents that modify risk factors for atherosclerosis (e.g., reduction of plasma lipids and anti-hypertensive agents), there are no therapies that directly modify the atherosclerosis process itself. Further, more than 60% of all coronary artery disease cannot be explained on the basis of traditional risk factors alone.

[0004] One explanation for the lack of success of current treatments for the above-mentioned diseases is that multiple gene products are probably involved in each disease or disorder. Typical drug therapies target only one of these gene products. Also, many of the current drugs used to treat these diseases and disorders exhibit undesirable side effects such as, for example, the gastric ulceration observed with many nonsteroidal anti-inflammatory drugs ("NSAIDs") used to treat arthritis. Disadvantages of surgical methods of treating these diseases and disorders include the use of highly invasive procedures that cause pain, scarring, and sometimes infection.

[0005] In contrast, inhibition of NF-κB is potentially capable of halting, and even reversing, the progression of the underlying diseases and disorders mentioned above. Inhibitors of NF-κB are effective by virtue of their ability to prevent, block, and even halt a common key step in the activation of the genes involved in the production of a number of mediators of these diseases and disorders. In other words, NF-κB inhibitors work upstream to inhibit the production of multiple pro-inflammatory mediators, whereas traditional drug treatment regimens are less effective, perhaps because they work downstream and typically target only one of these mediators.

[0006] Nuclear factor-κB is a family of heterogeneous protein dimers that act as sequence-specific transcription factors in the activation of a large number of genes in response to inflammation, viral or bacterial infections, or other biological diseases and disorders requiring rapid reprogramming of gene expression. NF-κB is normally found sequestered in the cytoplasm in an inactive form bound to an inhibitory protein, namely the inhibitor of κB ("IκB"). IκB is thus bound with NF-κB to form an NF-κB-IκB complex, but NF-κB is rapidly converted to an active form via signaling processes that are still being elucidated.

[0007] NF-κB is found in virtually all cell types including T-lymphocytes, monocytes, macrophages, endothelial cells, and smooth muscle cells. In response to a stimulus such as, for example, an inflammatory cytokine, a reactive oxygen intermediate, or a lipopolysaccharide from a microorganism, the IκB component of the NF-κB—IκB complex is cleaved via a process comprising the sequential steps of phosphorylation, polyubiquitinylation, and degradation. Degradation of the modified IκB protein exposes the nuclear localization sequence on NF-κB, allowing translocation of NF-κB to the nucleus of the cell, where it binds to its target gene to initiate transcription.

[0008] Among the genes to which NF-κB binds in order to initiate transcription are genes expressing pro-inflammatory cytokines. These pro-inflammatory cytokines include tumor necrosis factor-alpha ("TNF-α"), interleukin-1 ("IL-1"), IL-6, IL-8, intercellular adhesion molecule-1 ("ICAM-1"), vascular cell adhesion molecule-1 ("VCAM-1"), E-selectin, monocyte chemotactic protein-1 ("MCP-1"), inducible nitric oxide synthase, tissue factor, and cyclooxygenase-2 ("COX-2"). The result of the transcriptional activation of genes expressing pro-inflammatory cytokines is a tissue-localized production of these cytokines, and the beginning or exacerbation of an inflammatory process in the affected tissue.

[0009] The present invention provides a method of using a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, to treat diseases and disorders known to be responsive to the inhibition of NF-κB.

[0010] The following United States patents disclose methods of using certain sulfonylaminocarbonyl derivatives as inhibitors of the enzyme acyl-coenzyme A:cholesterol acyltransferase (ACAT) for treating hypercholesterolemia and atherosclerosis:

United States Patent Number 5,245,068 and its Divisional 5,384,328;
United States Patent Number 5,214,206 and its Divisional 5,288,757;
United States Patent Number 5,254,715 and its Divisional 5,336,690;
United States Patent Number 5,198,466 and its Divisional 5,364,882;
United States Patent Number 5,491,172 and its Divisional 5,633,287; and
United States Patent Number 5,254,589 and its Continuation 5,981,595.

[0011] United States Patent Number 6,093,744 discloses methods of using certain sulfonylaminocarbonyl derivatives as ACAT inhibitors for regulating plasma cholesterol levels and lowering serum or plasma Lp(a) levels, and for treating hypercholesterolemia, atherosclerosis, peripheral vascular diseases, and restenosis.

[0012] United States Patent Number 6,117,909 discloses methods of using certain sulfonylaminocarbonyl derivatives as ACAT inhibitors for lowering serum or plasma Lp(a) levels, and treating cerebrovascular diseases, including stroke, peripheral vascular diseases, and restenosis.

[0013] United States Patent Number 6,124,309 and its Divisional Patent Numbers 6,143,755 and 6,093,719 disclose methods of using a sulfonylaminocarbonyl derivative as an ACAT inhibitor in combination with an HMG-CoA reductase inhibitor for restoring endogenous vascular endothelium-dependent activities including improving the normal dilation capacity of the endothelium, inducing vasodilation to modulate vascular tone and blood flow, decreasing the adherent properties of the blood vessel walls, and decreasing the coagulation of platelets, and for treating myocardial infarction and acute ischemic syndromes including angina pectoris, coronary artery disease, hypertension, cerebrovascular accidents, transient ischemic attacks, chronic obstructive pulmonary disease, chronic hypoxic lung disease, pulmonary hypertension, renal hypertension, chronic renal disease, microvascular complications of diabetes, and vaso-occlusive complications of sickle cell anemia.

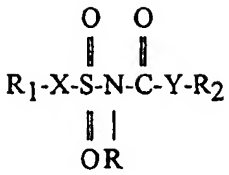
[0014] As NF-κB is involved in the initiation and progression of inflammatory disease, a screening assay which provides a method for rapidly screening large numbers of compounds in vitro for their ability to inhibit NF-κB mediated transcription of a gene would be a valuable tool. Such a screening assay would be an important step in the pursuit of compounds to treat diseases responsive to inhibition of NF-κB.

[0015] We have now discovered the ability of certain sulfonylaminocarbonyl derivatives to inhibit NF-κB mediated transcription. Accordingly, the present invention provides a method of treating a disease or a disorder responsive to inhibition of NF-κB, comprising administering to patients in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof. All that is needed to practice the present invention is to administer to said patients a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, from 1 to 6 times daily for the treatment of rheumatoid arthritis, osteoarthritis, autoimmune diseases, psoriasis, asthma, cardiovascular diseases such as, for example, atherosclerosis, acute coronary syndromes including myocardial infarction and unstable angina, and congestive heart failure, Alzheimer's disease, multiple sclerosis, cancer, type II diabetes, metabolic syndrome X, and inflammatory bowel disease. Determination of a proper dosage and form of administration of a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, for use in the method of the present invention is well within the abilities of one of ordinary skill in the pharmaceutical and medical arts.

SUMMARY OF THE INVENTION

[0016] The present invention provides a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof.

[0017] The sulfonylaminocarbonyl derivatives disclosed in United States Patent Number 5,491,172 and its Divisional 5,633,287, which are both hereby incorporated herein by reference, are useful in the present invention. Thus, one embodiment of the present invention is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

X and Y are selected from oxygen, sulfur and $(CR'R'')_n$, wherein n is an integer of from 1 to 4 and R' and R" are each independently hydrogen, alkyl, alkoxy, halogen, hydroxy, acyloxy, cycloalkyl, phenyl optionally substituted or R' and R" together form a spirocycloalkyl or a carbonyl; with the proviso at least one of X and Y is $-(CR'R'')_n-$ and with the further proviso when X and Y are both $(CR'R'')_n$ and R' and R" are hydrogen and n is one, R_1 and R_2 are aryl;
R is hydrogen, a straight or branched alkyl of from 1 to 8 carbon atoms or benzyl;
R_1 and R_2 are each independently selected from:

(a) phenyl or phenoxy each of which is unsubstituted or is substituted with from 1 to 5 substituents selected from:

phenyl,
an alkyl group having from 1 to 6 carbon atoms and which is straight or branched,
an alkoxy group having from 1 to 6 carbon atoms and which is straight or branched;
phenoxy,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl,
-COOH,
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched, and
$-(CH_2)_pNR_3R_4$, wherein p is zero or one, and each of R_3 and R_4 is selected from hydrogen or a straight or branched alkyl group having 1 to 4 carbon atoms;

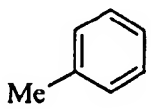
(b) 1- or 2-naphthyl unsubstituted or substituted with from 1 to 3 substituents selected from:

phenyl,
an alkyl group having from 1 to 6 carbon atoms and which is straight or branched,
an alkoxy group having from 1 to 6 carbon atoms and which is straight or branched;
hydroxy,
phenoxy,
fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl,
-COOH,
-COOalkyl, wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,
$-(CH_2)_pNR_3R_4$, wherein p, R_3 and R_4 have the meanings defined above;

(c) arylalkyl;
(d) a straight or branched alkyl chain having from 1 to 20 carbon atoms and which is saturated or contains from 1 to 3 double bonds; and
(e) adamantyl or a cycloalkyl group wherein the cycloalkyl moiety has from 3 to 6 carbon atoms; with the provisos:

(i) where X is $(CH_2)_n$, Y is oxygen, and R_1 is a substituted phenyl, then R_2 is a substituted phenyl;

(ii) where Y is oxygen, X is $(CH_2)_n$, R_2 is phenyl or naphthyl, then R_1 is not a straight or branched alkyl chain; and
(iii) the following compounds are excluded:

X	Y	R	R_1	R_2
CH_2	O	H	$(CH2)CH_3$	Ph
CH_2	O	H	CH_3	Ph
CH_2	O	H		i-Pr

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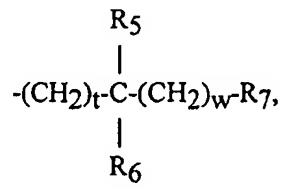
with the further proviso that compounds selected from the group consisting of:

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and
Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)phenyl ester are excluded.

[0018] Preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula I:

wherein R_1 is phenyl or is phenyl disubstituted in the 2,6-positions;
wherein R_2 is phenyl or is phenyl disubstituted in the 2,6-positions;
wherein each of R_1 and R_2 is phenyl;
wherein each phenyl is disubstituted in the 2,6-position;
wherein R_1 is phenyl disubstituted in the 2,6-positions and R_2 is phenyl trisubstituted in the 2,4,6-positions;
wherein R_1 is 2,6-bis(1-methylethyl)phenyl and R_2 is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl; or
wherein one of R_1 and R_2 is the group



wherein t is zero or 1 to 4; w is zero or 1 to 4 with the proviso that the sum of t and w is not greater than 5; R_5 and R_6 are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R_5 is hydrogen, R_6 can be selected from the groups defined for R_7; and R_7 is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, -COOH, COOalkyl wherein alkyl has from 1 to 4 carbon atoms, or $-(CH_2)_pNR_3R_4$ wherein P, R_3 and R_4 have the meanings defined above.

[0019] Preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula I, or a pharmaceutically acceptable salt thereof, wherein:

X is oxygen, sulfur or (CR'R")n;
Y is oxygen, sulfur or (CR'R")n, with the proviso that at least one of X or Y is (CR'R")n wherein n is an integer of

from 1 to 4 and R' and R" are each independently hydrogen, straight or branched alkyl of from 1 to 6 carbons, optionally substituted phenyl, halogen, hydroxy, alkoxy, acyloxy, cycloalkyl, or R' and R" taken together form a carbonyl or a spirocycloalkyl group of from 3 to 10 carbons;
R is hydrogen;
R_1 is phenyl optionally substituted, straight or branched alkyl of from 1 to 10 carbon atoms, cycloalkyl of from 3 to 10 carbon atoms; and
R_2 is phenyl optionally substituted, straight or branched alkyl of from 1 to 10 carbon atoms, cycloalkyl of from 3 to 8 carbon atoms, phenoxy optionally substituted with the proviso that only if X is $(CR'R")_n$ can R_1 be optionally substituted phenoxy and only if Y is $(CR'R")_n$ can R_2 be optionally substituted phenoxy, and with the further proviso that at least one of R_1 and R_2 is optionally substituted phenyl or phenoxy.

[0020] Preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula I, or a pharmaceutically acceptable salt thereof, wherein:

X is oxygen;
Y is $(CR'R")_n$ wherein n is an integer of from 1 to 2;
R is hydrogen;
R_1 is optionally substituted phenyl;
R_2 is optionally substituted phenyl or phenoxy, straight or branched alkyl of from 1 to 10 carbons, or cycloalkyl of from 3 to 10 carbons; and
R' and R" are each independently hydrogen, straight or branched alkyl of from 1 to 6 carbons, optionally substituted phenyl, halogen, hydroxy, alkoxy, acyloxy, cycloalkyl, or R' and R" taken together form a carbonyl or a spirocycloalkyl.

[0021] Preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula I, or a pharmaceutically acceptable salt thereof, wherein one of R_1 and R_2 is phenyl; and more preferably wherein one of R_1 and R_2 is substituted phenyl; or still more preferably wherein one of R_1 and R_2 is phenyl disubstituted in the 2,6-positions.

[0022] More preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula I, or a pharmaceutically acceptable salt thereof, wherein both R_1 and R_2 are phenyl disubstituted in the 2,6-positions.

[0023] In another more preferred embodiment, the method uses a sulfonylaminocarbonyl derivative of Formula I, or a pharmaceutically acceptable salt thereof, wherein R_1 is phenyl disubstituted in the 2,6-positions and R_2 is phenyl trisubstituted in the 2,4,6-positions.

[0024] Preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula I, or a pharmaceutically acceptable salt thereof, selected from:

(1,2,3,4-Tetrahydro-naphthalene-2-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester;
[Bis-(4-chloro-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester;
(Bromo-phenyl-acetyl)-sulfamic acid 2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-hydroxy-2,6-diisopropyl-phenyl ester;
Methyl-[(2,4,6-triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-nitrophenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-fluoro-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-dimethoxy-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-amino-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,4,6-trimethoxy-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-tert-butyl-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-acetyl-2-isopropylphenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-methoxy-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-dichloro-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid dodecyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-bromo-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-methyl-phenyl ester;

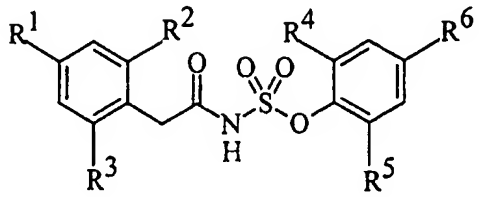
[1-(4-Dimethylamino-phenyl)-cyclopentanecarbonyl]-sulfamic acid 2,6-diisopropyl-phenyl ester;
[1-(4-Nitro-phenyl)-cyclopentanecarbonyl]-sulfamic acid 2,6-diisopropyl-phenyl ester;
3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-benzoic acid methyl ester;
Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methyl-ethyl)phenyl ester;
Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methyl-ethyl)phenyl ester;
Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl-2,4,6-tris(1-methyl-ethyl)phenyl ester;
Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,4,6-tris(1-methyl-ethyl)phenyl ester;
Sulfamic acid[adamantaneacetyl]-2,6-bis[1-methylethyl)phenyl ester,
Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methyl-ethyl)phenyl ester-sodium salt;
Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methyl-ethyl)phenyl ester-sodium salt;
Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester;
Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester;
2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]methyl]-sulfonyl]benzeneacetamide;
2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]methyl]-sulfonyl]benzeneacetamide-sodium salt;
2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]methyl]-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]methyl]-sulfonyl]carbamate-sodium salt;
Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester-sodium salt;
Sulfamic acid trans-[(2-phenylcyclopropyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)-phenyl ester;
Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)-phenyl ester;
Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-methylethyl)-phenyl ester;
Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-2,6-bis(1-methylethyl)-phenyl ester;
Sulfamic acid (1-oxo-2-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (cyclopentylphenyl-acetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (cyclohexylacetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (diphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (triphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [(1-phenylcyclopentyl)carbonyl]-2,6-bis(1-methylethyl)-phenyl ester;
Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (1-oxo-2-phenylbutyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (cyclohexylphenyl-acetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (1-oxo-2,2-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (1-oxo-3-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [(acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt;
Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester; and
Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester.

[0025] More preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula I named sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl-2,6-bis(1-methylethyl)phenyl ester, or a pharmaceutically acceptable salt thereof.

[0026] Still more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula I named sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl-2,6-bis(1-methylethyl)phenyl ester.

[0027] The sulfonylaminocarbonyl derivatives disclosed in United States Patent Number 6,093,744, which is hereby incorporated herein by reference, are also useful in the present invention. Thus, another embodiment of the present invention is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription

factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula II



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or a pharmaceutically acceptable salt thereof, wherein:

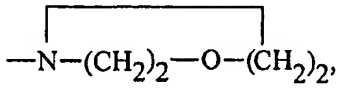
R^1 is hydrogen, alkyl, or alkoxy;
R^2 to R^5 are alkyl, alkoxy, or unsubstituted or substituted phenyl; and
R^6 is -CN,

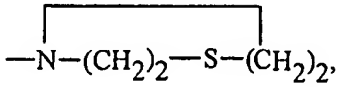
$-(CH_2)_{0-1}-NR^7R^8$,
$-O-(CH_2)_{1-10}-Z$, wherein Z is $-NR^9R^{10}$, OR^1, or CO_2R^1,
$-OC(=O)R^{11}$,
$-SR^{11}$,
-SCN,
$-S(CH_2)_{1-10}Z$,
$-S(O)_{1-2}R^{12}$, wherein R^{12} is hydroxy, alkoxy, alkyl, $(CH_2)_{1-10}Z$ or NR^7R^8,
$-C(=O)XR^{11}$, or
$-CH_2-R^{13}$, wherein R^{13} is $(CH_2)_{0-5}-Y-(CH_2)_{0-5}Z$, or alkyl of from 1 to 20 carbons with from 1-3 double bonds, which alkyl is optionally substituted by one or more moieties selected from -CN, NO_2, halogen, OR^1, NR^9R^{10}, and CO_2R^1;

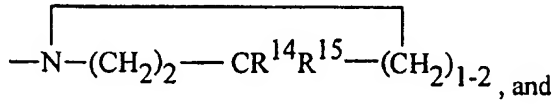
wherein R^7 and R^8 are each independently selected from:

- hydrogen, at least one of R^7 and R^8 is other than hydrogen;
- $(CH_2)_{1-10}Z$, wherein Z is as defined above and R^9 and R^{10} are each independently selected from hydrogen, alkyl, and unsubstituted or substituted phenyl, or

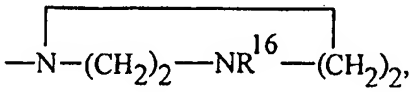
R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a ring selected from:







, and

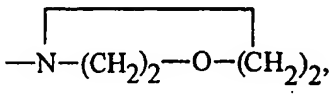


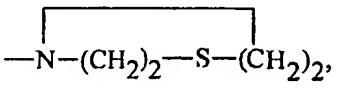
wherein R^{14}, R^{15}, and R^{16} are each independently selected from hydrogen, alkyl, and unsubstituted or substituted

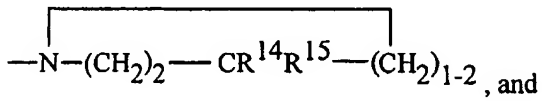
phenyl;

- $C(=Q)XR^{11}$, wherein X is a bond or NH wherein Q is O or S, R^{11} is hydrogen, alkyl, unsubstituted or substituted phenyl;
- $(CH_2)_{0-5}$-Y-$(CH_2)_{0-5}$Z, wherein Z is as defined above and Y is phenyl or a bond;
- $C(=O)$-$CR^{17}R^{18}Z$;
- $C(=O)NHCR^{17}R^{18}Z$, wherein R^{17} and R^{18} are each independently hydrogen, alkyl, phenyl, substituted phenyl, or the side chain of a naturally occurring amino acid;
- $S(O)_{1-2}R^{19}$, wherein R^{19} is alkyl, unsubstituted or substituted phenyl, naphthyl, or a heteroaromatic ring, or NR^9R^{10}; or

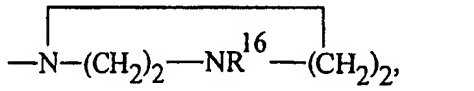
R^7 and R^8 are taken together with the nitrogen to which they are attached to form a ring selected from:







and



wherein R^{14}, R^{15}, and R^{16} are as above, with the proviso that compounds selected from:

[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-formyl-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-cyano-vinyl)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(4-methyl-piperazin-1-ylmethyl)-phenyl ester, dihydrochloride;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[bis-(2-hydroxyethyl)-amino]-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(3-phenyl-thioureido]-phenyl ester; and
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-sulfamoyl-phenyl ester are excluded.

[0028] Preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula II, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or alkyl of from 1 to 4 carbon atoms;
R^2 to R^5 are each alkyl of from 1 to 4 carbon atoms; and
R^6 is $-NR^7R^8$ wherein R^7 and R^8 are each independently selected from:

hydrogen, at least one of R^7 and R^8 is not hydrogen,
$-(CH_2)_{1-10}Z$,
$-C(=Q)XR^{11}$, or
$-S(O)_{1-2}R^{19}$.

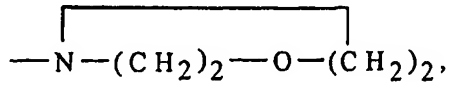
[0029] More preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of For-

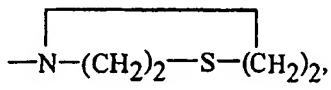
mula II, or a pharmaceutically acceptable salt thereof, wherein:

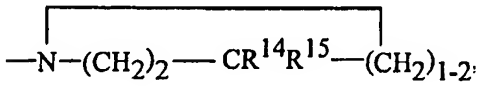
R^7 is hydrogen and
R^8 is $-C(=O)CR^{17}R^{18}Z$ wherein Z is NH_2 where one of R^{17} and R^{18} is the side chain of a naturally occurring amino acid and the other is hydrogen.

[0030] Also preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula II, or a pharmaceutically acceptable salt thereof, wherein:

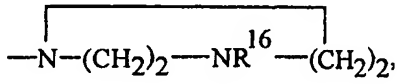
R^1 is hydrogen or alkyl of from 1 to 4 carbon atoms;
R^2 to R^5 are each alkyl of from 1 to 4 carbon atoms; and
R^6 is NR^7R^8, wherein R^7 and R^8 taken together with the nitrogen to which they are attached to form a ring selected from the group consisting of:







wherein R^{14} and R^{15} are each independently selected from hydrogen, alkyl, and phenyl; and



wherein R^{16} is hydrogen, alkyl, or phenyl.

[0031] Also preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula II, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or alkyl of from 1 to 4 carbon atoms;
R^2 to R^5 are each alkyl of from 1 to 4; and
R^6 is NR^7R^8, wherein one of R^7 and R^8 is hydrogen and the other is $S(O)_{1-2}R^{19}$

wherein R^{19} is alkyl, unsubstituted or substituted phenyl, naphthyl, or a heteroaromatic ring.

[0032] More preferred is the invention method using a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or alkyl of from 1 to 4 carbons;
R^2 to R^5 are alkyl of from 1 to 4 carbons; and
R^6 is $-C(=O)XR^{11}$ or $-CH_2R^{13}$ wherein X, R^{11}, and R^{13} are as defined above for Formula II.

[0033] Also preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula II, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or alkyl of from 1 to 4 carbon atoms;
R^2 to R^5 are alkyl of from 1 to 4 carbon atoms; and
R^6 is $-O-(CH_2)_{1-10}Z$,

$-O-C(=O)R^{11}$,
-SH,
-SCN,
$-S(CH_2)_{1-10}Z$, or
$-S(O)_{1-2}R^{12}$ wherein Z, R^{11}, and R^{12} are as defined above for Formula II.

[0034] Also preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula II, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or alkyl of from 1 to 4 carbon atoms;
R^2 to R^5 are alkyl of from 1 to 4 carbon atoms; and
R^6 is $O(CH_2)_{1-10}NR^9R^{10}$ wherein R^9 and R^{10} are as defined above for Formula II.

[0035] Especially preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative of Formula II, or a pharmaceutically acceptable salt thereof, selected from:

6-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenyl)-hexanoic acid ethyl ester;
3-[3-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenyl)-ureido]-propionic acid ethyl ester;
{[4-(1-Hydroxy-1-methyl-ethyl)-2,6-diisopropyl-phenyl]-acetyl} -sulfamic acid 2,6-diisopropyl-phenyl ester;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-4-methyl-pentanoylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-tert-butyl-ureido)-2,6-diisopropyl-phenyl ester;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-amino-propionylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-cyano-vinyl)-2,6-diisopropyl-phenyl ester;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-3-hydroxy-propionylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-4-carbamoyl-butyrylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-3-methyl-butyrylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[3-(3,5-dichlorophenyl)-thioureido]-2,6-diisopropyl-phenyl ester;
(S)-[5-tert-Butoxycarbonylamino-5-(3,5-diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenyl-carbamoyl)-pentyl]-carbamic acid tert-butyl ester;
(S)-[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2,6-diaminohexanoylamino)-2,6-diisopropyl-phenyl ester dihydrochloride;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-t-butoxycarbonylamino-acetylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-acetylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-t-butoxycarbonylamino-4-methylsulfanyl-butyrylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-4-methylsulfanyl-butyrylamino)-2,6-diisopropyl-phenyl ester trifluoroacetate;
3-[3-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenyl)-ureido]-propionic acid ethyl ester;
3-[3-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenyl)-ureido]-propionic acid;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[2-amino-3-(1H-indol-3-yl)-propionylamino]-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(5-amino-pentanoylamino)-2,6-diisopropyl-phenyl ester trifluoroacetate(1:1)(salt);

(D)-[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-propionylamino)-2,6-diisopropyl-phenyl ester trifluoroacetate(1:1)(salt);
(L)-[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-propionylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-2-methyl-propionylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-dimethylamino-propoxy)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-dimethylamino-propoxy)-2,6-diisopropyl-phenyl ester hydrochloride salt;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-amino-propoxy)-2,6-diisopropyl-phenyl ester hydrochloride salt;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-thiocyanato-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-cyano-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[(2-amino-acetylamino)-methyl]-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(benzylamino-methyl)-2,6-diisopropyl-phenyl ester mono hydrochloride;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-carbamoyl-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-hydroxymethyl-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-acetylamino-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-hydroxyethylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[3-(2,6-diisopropylphenyl)-ureido]-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(3-phenyl-ureido]-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(thiophene-2-sulfonylamino)-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(5- dimethylaminonaphthalene-1-sulfonylamino)- 2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-methanesulfonylamino-phenyl ester;
6-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl-acetyl]sulfamoyloxy}-phenyl)-hexanoic acid ethyl ester; and
6-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl-acetyl]sulfamoyloxy}-phenyl)-hexanoic acid.

[0036] Also preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative or a pharmaceutically acceptable salt thereof selected from:

(9H-Xanthene-9-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester;
((E)-2-Methyl-3-phenyl-acryloyl)-sulfamic acid 2,6-diisopropyl-phenyl ester; and
(2-Oxo-2H-chromene-3-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester.

[0037] The sulfonylaminocarbonyl derivatives disclosed in United States Patent No. 5,254,715 and its divisional 5,336,690, which are both hereby incorporated herein by reference, are also useful in the present invention. Thus, another embodiment of the present invention is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative selected from:

Carbamic acid, [(phenylamino)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [(phenylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-hydroxyphenyl ester;
Carbamic acid, [(phenylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-phenyl ester;
Carbamic acid, [(didecylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester;
Carbamic acid, [[bis(1-methylethyl)amino]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [(dipentylamino)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[(diphenylmethyl)amino]sulfonyl]methyl-, 2,6-bis(1,1-dimethylethyl)phenyl ester;
DL-Tryptophan,]a/-methyl-N-[[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]sulfonyl]-, methyl ester;
Carbamic acid, sulfonylbis-, bis[2,6-bis(1-methylethyl)phenyl] ester;
Carbamic acid, [[[2-(phenylmethyl)phenyl]amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)phenyl ester;
Methyl[[2,6-bis(1-methylethyl)phenyl amino]sulfonyl]carbamate;
Dodecyl[[2,6-bis(1-methylethyl)phenyl] amino]sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methoxyphenyl[[(2,2-diphenylethyl)amino]-sulfonyl] carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methoxy phenyl [[[2,6-bis(1-methylethyl)-phenyl]amino]sulfonyl] carbamate;
2,6-Bis(1,1-dimethylethyl)phenyl-[[(diphenylmethyl)amino]-sulfonyl]carbamate;

2,6-Bis(1,1-dimethylethyl)phenyl [[[2,6-bis(1-methylethyl)phenyl]amino]-sulfonyl] carbamate;
2,6-Bis(1,1-dimethylethyl)phenyl [[(2,2-diphenylethyl)amino]sulfonyl]-carbamate;
2,6-Bis(1,1-dimethylethyl)phenyl [[bis(phenylmethyl)amino]sulfonyl]-carbamate;
2,6-bis(1-methylethyl)phenyl[(diphenyl-amino)sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[(dibutyl-amino)sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[[bis(phenyl-methyl)amino]sulfonyl]-carbamate;
2,6-Bis(1-methylethyl)phenyl[(1H-benzimidazol-2-ylamino)sulfonyl]-carbamate;
2,6-Bis(1-methylethyl)phenyl[[2,2-diphenylethyl)amino]sulfonyl]-carbamate;
2,6-Bis(1-methylethyl)phenyl[[[2,6-bis(1-methylethyl)phenyl]amino]-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[[(diphenyl-methyl)amino] sulfonyl]-carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[(diphenylmethyl)amino]-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[[bis(2,6-bis(1-methylethyl)-phenyl]amino] sulfonyl] carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[(2,2-diphenylethyl)amino]-sulfonyl]-carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl [(dibutylamino)sulfonyl]-carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl [(dipentylamino)sulfonyl]-carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl [[bis(1-methylethyl)amino]-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[(dihexylamino)sulfonyl]-carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl [(hexylamino)sulfonyl]-carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[methyl(2-phenylethyl)-amino] sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[[bis-3-(dimethylamino)-propyl]amino]-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[(methyl octyl amino)-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-[[bis[(tetrahydro-2-furanyl)methyl]-amino]sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[(dioctylamino)sulfonyl]-carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[[methyl 2-(2-pyridinyl)-ethyl]amino]sulfonyl]carbamate; hydrochloride salt,
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[[methyl 2-(2-pyridinyl)-ethyl]amino]-sulfonyl]carbamate, sodium salt,
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[(dodecylamino)sulfonyl]-carbamate;
2,6-Bis(1-methylethyl)phenyl[[bis(1-methylethyl)amino]sulfonyl]-carbamate;
2,6-Bis(1-methylethyl)phenyl[[(1-methylethyl)phenylmethyl)amino]-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[(hexyl-amino)sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[(dioctyl-amino)sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[[cyclo-hexyl(1-methylethyl)amino]-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[(methyl-octylamino)sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[(dihexyl-amino)sulfonyl]carbamate;
Dodecyl[[(2,4,6-trimethoxyphenyl)amino]-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl ester(4-morpholinylsulfonyl)carbamic acid,
2,6-Bis(1-methylethyl)phenyl ester(1-piperidinylsulfonyl)carbamic acid;
2,6-Bis(1-methylethyl)phenyl ester(1-pyrrolidinylsulfonyl)carbamic acid;
2,6-Bis(1-methylethyl)phenyl ester[(2,3-dihydro- 1H-indol-1-yl)sulfonyl]-carbamic acid;
2,6-Bis(1-methylethyl)phenyl[(dibutylamino)sulfonyl]carbamate monosodium salt; and
2,6-Bis(1,1-dimethylethyl)phenyl[[(diphenylmethyl)amino]sulfonyl]-methyl carbamate.

[0038] The sulfonylaminocarbonyl derivatives disclosed in United States Patent No. 5,214,206 and its divisional 5,288,757, which are both hereby incorporated hereln by reference, are also useful in the present invention. Thus, another embodiment of the present invention is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative selected from:

Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dipropylamino)sulfonyl]-;
Urea, N-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N'-[[(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]sulfonyl]-, (4S-*cis*)-;
Urea, N-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N'-[[(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)amino]sulfonyl]-, stereoisomer;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis(1-methylethyl)amino]-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(diphenylmethyl)amino]-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(diphenylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dibutylamino)sulfonyl]urea;
N-[[[2,6-bis(1-methylethyl)phenyl] amino]-sulfonyl]-N'-(diphenylmethyl)-urea;

N-[2,6-bis(1-methylethyl)phenyl]-N'-[[[2,6-bis(1-methylethyl)phenyl]-amino]sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(2,2-diphenylethyl)amino]-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(9H-fluoren-9-ylamino)sulfonyl]-urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis(phenylmethyl)amino]sulfonyl]-urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(1-methylethyl)(phenylmethyl)-amino] sulfonyl] urea;
N-[2,6-bis(1-methylethyl)phenyl)-N'-[(dioctylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(4-phenyl- 1-piperidinyl)-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dihexylamino)sulfonyl]urea;
N-[[bis[3-(dimethylamino)propyl]amino]-sulfonyl]-N'-[2,6-bis(1-methylethyl)phenyl] urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(hexylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis-[(tetrahydro-2-furanyl)methyl]amino]sulfonyl]-urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(diethylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(methyloctyl amino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[cyclohexyl(1-methylethyl)amino]-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dipentylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis(2-methylpropyl)amino]-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[ethyl(2-propenyl)amino]-sulfonyl]urea;
N-[[bis(3-methylbutyl)amino] sulfonyl]-N'-[2,6-bis(1-methylethyl)-phenyl]urea;
N-[2,6-bis(1-methylethyl)phenyl)-N'-[(didecylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(didodecylamino)sulfamoyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(diisopropylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dicyclohexylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(methyloctadecylamino)-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(di-2-propenylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(1;1-dimethylethyl)(1-methylethyl)amino]sulfonyl]-urea;
N-[2,6-bis(1 -methylethyl)phenyl]-N'-[[bis(1-methylpropyl)amino]-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(methyltetradecylamino)-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-pyrrolidinylsulfonyl) urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-piperidinylsulfonyl) urea;
N'-[[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-N;N-bis(phenylmethyl) urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dibutylamino)sulfonyl]urea; monosodium salt; and
N'-[2,6-bis(1-methylethyl)phenyl]-N-methyl-[(dibutylamino)sulfonyl]urea.

[0039] The sulfonylaminocarbonyl derivatives disclosed in United States patent no. 5,198,466 and its divisional 5,364,882, which are both hereby incorporated herein by reference, are also useful in the present invention. Thus, another embodiment of the present invention is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative selected from:

Sulfamic acid, [[[2,4,6-tris(1-methylethyl)phenyl]amino]-carbonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid, [[[[1-[4-(dimethylamino)phenyl]cyclopentyl]methyl]-amino]carbonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
(2,3-Dihydro-indole- 1-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester;
Sulfamic acid, [[(triphenylmethyl)amino]carbonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Octadecyl [[[2,6-bis(1-methylethyl)phenyl]-amino]carbonyl]sulfamate;
Dodecyl-N-[[[2,6-bis(1-methylethyl)phenyl]-amino]carbonyl]sulfamate;
Decyl [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]sulfamate;
(±) 1-Methylheptyl [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]-sulfamate;
2,6-Bis(1-methylethyl)phenyl [[[2,6-bis(1-methylethyl)phenyl]amino]-carbonyl]sulfamate;
(±) 1-Methylundecyl [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]-sulfamate; and
Dodecyl [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]sulfamate, sodium salt.

[0040] The sulfonylaminocarbonyl derivatives disclosed in United States Patent No. 5,245,068 and its divisional 5,384,328, which are both hereby incorporated herein by reference, are also useful in the present invention. Thus, another embodiment of the present invention is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative selected from:

Carbamic acid, [(dodecyloxy)sulfonyl]-, dodecyl ester;
Carbamic acid, [(dodecyloxy)sulfonyl]-, [1,1':3',1"-terphenyl]-2'-yl ester;
Carbamothioic acid, [(dodecyloxy)sulfonyl]-, S-[2,6-bis(1-methylethyl)-phenyl] ester;
Carbamic acid, (phenoxysulfonyl)-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [(2,6-dimethylphenoxy)sulfonyl]-, 2,6-bis(1-methylethyl)-phenyl ester;
Carbamic acid, [[2,6-bis(1,1-dimethylethyl)phenoxy]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1,1-dimethylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [(2,6-difluorophenoxy)sulfonyl]-, 2,6-bis(1-methylethyl)-phenyl ester;
Carbamic acid, [(hexadecyloxy)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-dimethoxyphenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 1-methylheptyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)-4-nitrophenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 1,2-ethanediyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 1,2,3-propanetriyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-bromo-2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, [1,1':3',1"-terphenyl]-2'-yl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1,1dimethylethyl)-4-methoxyphenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-fluoro-2,3,5,6-tetrakis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-chloro-2,6-bis(1-methylethyl)phenyl ester;
Stigmasta-5,22-dien-3-ol, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-carbamate, (3α)-;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester;
Stigmastan-3-ol, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]carbamate, (3α)-;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-methoxy-2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4,6-tris(1-methylethyl)phenyl ester;
Carbamic acid, [[2,4,6-tris(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,4,6-tris(1-methylethyl)phenoxy]sulfonyl]-, 2,4,6-tris(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4,6-tris(1,1-dimethylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]dithio]-2,6-bis(1,1-dimethylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-[(dimethylamino)methyl]-2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-hydroxy-2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, cyclohexyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 3,3',5,5'-tetrakis(1-methylethyl)[1,1'-biphenyl]-4,4'-diyl ester;
Carbamic acid, [[4-hydroxy-2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, tricyclo[3.3.1.1^{3,7}]dec-1-yl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2-(1,1-dimethylethyl)-6-methylphenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 5-methyl-2-(1-methylethyl)cyclohexyl ester;
Carbamothioic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, *S*-[2,6-bis(1-methylethyl)phenyl] ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, (2,6-diethylphenyl)methyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, (2*S*,6*S*)-2,6-bis(1-methylethyl)cyclohexyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-(1,1-dimethylethyl)-2,6-(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-fluorophenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4-difluorophenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, pentafluorophenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-difluorophenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, (2*R*,6*S*)-2,6-bis(1-methylethyl)cyclohexyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,3,5,6-tetramethylphenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 3-pyridinyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-dimethylphenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-acetyl-2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-fluoro-2,6-bis(1-methylethyl)phenyl ester;
2,6-Bis(1-methylethyl)phenyl[[2,6-bis(1-methylethyl)phenoxy]-sulfonyl]-carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methylphenyl (phenoxysulfonyl)carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methylphenyl[(hexyloxy)sulfonyl]carbamate;

2,6-Bis(1,1-dimethylethyl)-4-methylphenyl[(dodecyloxy-sulfonyl]-carbamate;
Dodecyl [[2,6-bis(1-methylethyl)phenoxy]-sulfonyl]carbamate;
Methyl[[2,6-bis(1-methylethyl)phenoxy]-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[(hexyloxy)-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl](dodecyloxy)-sulfonyl]carbamate; and
2,6-Bis(1,1-dimethylethyl)phenyl[[2,6-bis(1-methylethyl)phenoxy]-sulfonyl]carbamate.

[0041] The sulfonylaminocarbonyl derivatives disclosed in United States Patent No. 5,254,589 and its continuation 5,981,595, which are both hereby incorporated herein by reference, are also useful in the present invention. Thus, another embodiment of the present invention is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative selected from:

N-[2,6-bis(1-methylethyl)phenyl]-N'-(6-ethoxy-2-benzothiazolyl)-sulfonyl]-urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-octadecylsulfonyl)urea;
N-[2,4,6-triemthoxyphenyl]-N'-(2-octadecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(tetradecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-methyl-N'-(tetradecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(dodecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(hexadecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-methyl-N'-(dodecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(tridecylsulfonyl)urea;
N-[2,4,6-trimethoxyphenyl]-N'-(hexadecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-methyl-2-pentadecylsulfonyl)urea;
N-2,6-bis(1-methylethyl)phenyl-N'-(dodecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-phenyl-1-tetradecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-phenyl-1-nonylsulfonyl)urea; and
N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-decylsulfonyl)urea.

[0042] The following sulfonylaminocarbonyl derivatives are excluded from use in the methods of the present invention:

Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dimethylamino)sulfonyl]-;
Sulfamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]-, hexyl ester;
Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[[methyl(2-phenylethyl)-amino]sulfonyl]-;
Carbamic acid, [(4-methyl-1-piperazinyl)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester, monohydrochloride;
Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(butylmethylamino)sulfonyl]-;
Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(1-methylethyl)amino]-sulfonyl]-;
Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(butylethylamino)sulfonyl]-;
Carbamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-, [1,1':3',1"-terphenyl]-2'-yl ester;
Carbamic acid, [(2,6-dimethoxyphenoxy)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [(2,4-difluorophenoxy)sulfonyl]-, 2,6-bis(1-methylethyl)-phenyl ester;
Carbamic acid, [(2,4,6-trimethoxyphenoxy)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [(2,6-dimethoxyphenoxy)sulfonyl]-, 2,6-dimethoxyphenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]methyl-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, ethyl ester, sodium salt;
[3-(2,4,6-Triisopropyl-phenyl)-propionyl)-sulfamic acid 2,6-diisopropyl-phenyl ester;
[Fluoro-(2,4,6-triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid [1,1';3',1"]terphenyl-2'-yl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-chlorophenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, (3-pyridinyl)methyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-chloro-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(3-phenyl-thioureido)-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-formyl-2,6-diisopropyl-phenyl ester;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((R)-2-amino-4-methyl-pentanoylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[bis-(2-hydroxyethyl)-amino]-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-sulfamoyl-phenyl ester;

Benzeneacetamide, N-[[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-2,4,6-tris(1-methylethyl)-;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(4-methyl-piperazin-1-ylmethyl)-phenyl ester; compound with generic inorganic neutral component;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-aminomethyl-2,6-diisopropyl-phenyl ester; compound with generic inorganic neutral component;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-3-phenyl-proplonylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-3-methyl-pentanoylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
(2,3-Diphenyl-acryloyl)-sulfamic acid 3,4-dichloro-phenyl ester;
(4-Phenyl-but-3-enoyl)-sulfamic acid 2,6-diisopropyl-phenyl ester;
N-[2,6-bis(1-methylethyl)phenyl]-N'-phenylmethyl-N'-(tetradecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(octylsulfonyl)urea;
N-(2,4-difluorophenyl)-N'-(tetradecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(decylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-pentadecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl)-N'-[[6-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)hexyl]sulfonyl]urea;
N-[[[2,6-bis(1-methylethyl)phenyl]amino-carbonyl]-14-heptacosanesulfonamide; and
N-[2,4,6-trimethoxyphenyl]-N'-(tetradecylsulfonyl)urea.

[0043] Another embodiment of the invention is a method of inhibiting NF-κB transcription factors in an animal, comprising administering to the animal an NF-κB inhibiting amount of a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof.

[0044] Another invention embodiment is use of a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors.

[0045] Another invention embodiment is a pharmaceutical composition, comprising a nuclear factor-κB transcription factor inhibiting amount of a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof.

[0046] Another embodiment of the present invention is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof,
wherein the disease or disorder being treated is rheumatoid arthritis, osteoarthritis, an autoimmune disease, psoriasis, asthma, a cardiovascular disease, an acute coronary syndrome, congestive heart failure, Alzheimer's disease, multiple sclerosis, cancer, type II diabetes, metabolic syndrome X, or inflammatory bowel disease.

[0047] Preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Grave's disease, myasthenia gravis, insulin resistance, autoimmune hemolytic anemia, scleroderma with anti-collagen antibodies (Abs), pernicious anemia, diabetes mellitus, psoriasis, asthma, atherosclerosis, myocardial infarction, unstable angina, congestive heart failure, Alzheimer's disease, multiple sclerosis, cancer, type II diabetes, metabolic syndrome X, or inflammatory bowel disease.

[0048] More preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is rheumatoid arthritis.

[0049] Also more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is osteoarthritis.

[0050] Also more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is insulin resistance.

[0051] Also more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is asthma.

[0052] Also more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is atherosclerosis.

[0053] Also more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or

a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is myocardial infarction.

[0054] Also more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is unstable angina.

[0055] Also more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is congestive heart failure.

[0056] Also more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is Alzheimer's disease.

[0057] Also more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is cancer.

[0058] Also more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is inflammatory bowel disease.

[0059] Also more preferred is a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is multiple sclerosis.

[0060] Also more preferred is the invention method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is type II diabetes.

[0061] Also more preferred is the invention method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transcription factors, comprising administering to a patient in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder being treated is metabolic syndrome X.

[0062] Another embodiment of the present invention is a method for screening compounds in vitro for their ability to inhibit NF-κB mediated transcription of a gene, comprising analyzing an assay mixture containing stimulated NF-κB using fluorescence detection.

[0063] Preferred is a method for screening compounds in vitro for their ability to inhibit NF-κB mediated transcription of a gene, comprising analyzing an assay mixture containing stimulated NF-κB using fluorescence detection wherein the assay is a cell-based assay.

[0064] Also preferred is a method for screening compounds in vitro for their ability to inhibit NF-κB mediated transcription of a gene, comprising analyzing an assay mixture containing stimulated NF-κB using fluorescence detection, wherein the assay is a cell-based assay and is performed in high throughput screening mode.

[0065] More preferred is a method for screening compounds in vitro for their ability to inhibit NF-κB mediated transcription of a gene, comprising analyzing an assay mixture containing stimulated NF-κB using fluorescence detection, the assay comprising:

Step a) Stably transfecting into cells an NF-κB binding site and a plasmid vector containing cDNA for an enzyme capable of cleaving a nonfluorescent substrate to produce a fluorescent cleavage product, an enzyme capable of cleaving a fluorescent substrate to produce a nonfluorescent cleavage product, or an enzyme capable of cleaving a fluorescent substrate to produce a fluorescent cleavage product;
Step b) Plating the cells of Step a) in media;
Step c) Incubating the mixture of plated cells of Step b);
Step d) Stimulating the cells of Step c) with a cytokine or a mixture of a cytokine and a compound being tested for NF-κB inhibition;
Step e) Adding a fluorescent disclosing reagent to the stimulated cells of Step d); and
Step f) Analyzing the mixture of Step e) by fluorescence detection.

[0066] Still more preferred is a method for screening compounds in vitro for their ability to inhibit NF-κB mediated transcription of a gene, comprising analyzing an assay mixture containing stimulated NF-κB using fluorescence detection, the assay comprising:

Step a) Stably transfecting into cells an NF-κB binding site and a plasmid vector containing cDNA for an enzyme capable of cleaving a nonfluorescent substrate to produce a fluorescent cleavage product, an enzyme capable of

cleaving a fluorescent substrate to produce a nonfluorescent cleavage product, or an enzyme capable of cleaving a fluorescent substrate to produce a fluorescent cleavage product;
Step b) Plating the cells of Step a) in media;
Step c) Incubating the mixture of plated cells of Step b);
Step d) Stimulating the cells of Step c) with a cytokine or a mixture of a cytokine and a compound being tested for NF-κB inhibition;
Step e) Adding a fluorescent disclosing reagent to the stimulated cells of Step d); and
Step f) Analyzing the mixture of Step e) by fluorescence detection,

wherein:

the cells undergoing transfection in Step a) are ECV-304 cells;
the cDNA being transfected in Step a) codes for β-lactamase;
the NF-κB binding site being transfected in Step a) is an HIV NF-κB binding site;
the cytokine employed in Step c) is TNF-α or IL-1β; or
the fluorescent disclosing reagent employed in Step e) is a CCF2 dye.

DETAILED DESCRIPTION OF THE INVENTION

[0067] As discussed above, the present invention provides a method of treating a disease or a disorder responsive to inhibition of nuclear factor-κB transciption factors comprising administering to patients in need thereof a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof.

[0068] While as mentioned above, some of the sulfonylaminocarbonyl derivatives useful in the methods of the present invention are also inhibitors of the enzyme ACAT, and accordingly have demonstrated serum and plasma cholesterol and Lp(a) regulating activities in vivo, no connection exists between these activities and the ability of the sulfonylaminocarbonyl derivatives to inhibit NF-κB mediated transcription and thereby treat diseases and disorders responsive to inhibition of NF-κB.

[0069] In Formula I above, illustrative examples of straight or branched saturated hydrocarbon chains having from 1 to 20 carbon atoms include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-undecyl, n-dodecyl, n-hexadecyl, 2,2-dimethyldodecyl, 2-tetradecyl, and n-octadecyl groups.

[0070] Illustrative examples of straight or branched hydrocarbon chains having from 1 to 20 carbon atoms and having from 1 to 3 double bonds include ethenyl, 2-propenyl, 2-butenyl, 3-pentenyl, 2-octenyl, 5-nonenyl, 4-undecenyl, 5-heptadecenyl, 3-octadecenyl, 9-octadecenyl, 2,2-dimethyl-11-eicosenyl, 9,12-octadecadienyl, and hexadecenyl.

[0071] Straight or branched alkoxy groups having from 1 to 6 carbon atoms include, for example, methoxy, ethoxy, n-propoxy, t-butoxy, and pentyloxy.

[0072] Illustrative examples of straight or branched alkyl groups having from 1 to 6 carbon atoms as used in Formula I include methyl, ethyl, n-propyl, isopropyl, n-pentyl, n-butyl, and tert-butyl.

[0073] Illustrative examples of cycloalkyl groups, as used in Formula I, include cyclopentyl, cyclohexyl, cyclooctyl, tetrahydronaphthyl, and 1- or 2-adamantyl.

[0074] Spirocycloalkyl groups are, for example, spirocyclopropyl, spirocyclobutyl, spirocyclopentyl, and spirocyclohexyl.

[0075] Illustrative examples of arylalkyl groups are: benzyl, phenethyl, 3-phenylpropyl, 2-phenylpropyl, 4-phenylbutyl, 2-phenylbutyl, 3-phenylbutyl, benzhydryl, 2,2-diphenylethyl, and 3,3-diphenylpropyl.

[0076] In Formula II above, illustrative examples of straight or branched carbon chains having from 1 to 10 carbon atoms include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, and n-octyl.

[0077] Alkoxy means straight or branched groups having from 1 to 6 carbon atoms include, for example, methoxy, ethoxy, n-propoxy, t-butoxy, and pentyloxy.

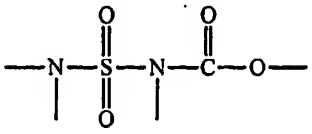
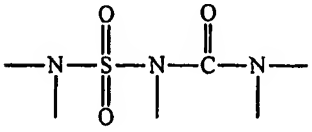
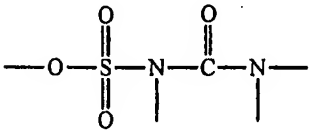
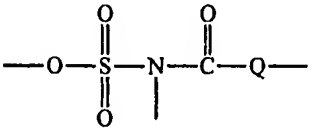
[0078] The natural (essential) amino acids are: valine, leucine, isoleucine, threonine, methionine, phenylalanine, tryptophan, lysine, alanine, aginine, aspartic acid, cysteine, glutamic acid, glycine, histidine, proline, serine, tyrosine, asparagine, and glutamine.

[0079] Preferred natural amino acids are: valine, leucine, isoleucine, threonine, lysine, alanine, glycine, serine, asparagine, and glutamine.

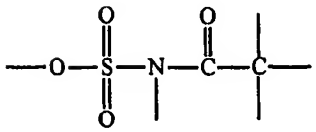
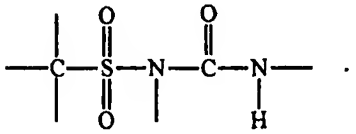
[0080] Phenyl, naphthyl, and heteroaromatic rings are unsubstituted or substituted by from 1 to 5 substituents selected from alkyl of from 1 to 6 carbons, alkoxy, halogen, nitro, cyano, carboxylic acids and alkyl esters, amino, and hydroxyl.

[0081] Heteroaromatic rings are, for example, 2-, 3-, or 4-pyridinyl; 2-, 4-, or 5-pyrimidinyl; 2- or 3-thienyl; isoquinolines, quinolines, pyrroles, indoles, and thiazoles.

[0082] The phrase "sulfonylaminocarbonyl derivative" means a compound with one of the following substructure motifs:

Motif Letter	Motif Substructure
A	
B	
C	
D	

wherein Q is O or S

E	
F	

[0083] United States Patent No. 5,254,715 and its divisional 5,336,690 describe sulfonylaminocarbonyl derivatives with substructure motif A.

[0084] United States Patent No. 5,214,206 and its divisional 5,288,757 describe sulfonylaminocarbonyl derivatives with substructure motif B.

[0085] United States Patent No. 5,198,466 and its divisional 5,364,882 describe sulfonylaminocarbonyl derivatives with substructure motif C.

[0086] United States Patent No. 5,245,068 and its divisional 5,384,328 describe sulfonylaminocarbonyl derivatives with substructure motif D.

[0087] United States Patent No. 5,491,172 and its divisional 5,633,287, and United States Patent No. 6,093,744 describe sulfonylaminocarbonyl derivatives with substructure motif E.

[0088] United States Patent No. 5,254,589 and its continuation 5,981,595 describe sulfonylaminocarbonyl deriva-

tives with substructure motif F.

[0089] The phrase "NF-κB inhibiting amount" means an amount of a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof, sufficient to inhibit a NF-κB transcription factor in a particular animal or animal population. For example in a human or other mammal, an NF-κB inhibiting amount can be determined experimentally in a laboratory setting by measuring NF-κB activity in vitro according to the methods described below. Alternatively, an NF-κB inhibiting amount can be determined in vivo in an animal being treated by measuring disease-modifying affects in the conventional way. In a clinical setting, an NF-κB inhibiting amount may be determined according to the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular NF-κB transcription factor being inhibited and patient being treated.

[0090] The phrase "autoimmune disease" means the diseases classified as "Highly probable" or "Probable" in TABLE 20-3. PUTATIVE AUTOIMMUNE DISORDERS of The Merck Manual of Diagnosis and Therapy, 16th edition, Robert Berkow ed., Merck Research Laboratories, Rahway, New Jersey, 1992, page 340, which is hereby incorporated herein by reference. Diseases classified as highly probable include, to name a few, systemic lupus erythematosus, Grave's disease, myasthenia gravis, insulin resistance, and autoimmune hemolytic anemia. Diseases classified as probable include, to name a few, rheumatoid arthritis, scleroderma with anti-collagen antibodies (Abs), pernicious anemia, and some cases of diabetes mellitus.

[0091] Examples of a cardiovascular disease include, but are not limited to, atherosclerosis and acute coronary syndrome.

[0092] Examples of an acute coronary syndrome include, but are not limited to, myocardial infarction and unstable angina.

[0093] The term "patient" means a mammal, including a human, cat, dog, sheep, pig, horse, and cow.

[0094] The term "animal" means a mammal, including a human, cat, dog, sheep, cow, horse, pig, rat, mouse, guinea pig, rabbit, monkey, and transgenic variants thereof.

[0095] The term "comprising," which is synonymous with the terms "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps from the scope of the invention that follows.

[0096] The phrase "consisting of" is closed-ended and excludes any element, step, or ingredient not specified in the description of the invention that follows.

[0097] The phrase "consisting essentially of" limits the scope of the invention that follows to the specified elements or steps and those further elements or steps that do not materially affect the basic and novel characteristics of the invention.

[0098] Some of the compounds useful in the present invention may have chiral centers, in which case all stereoisomers thereof, both individual stereoisomers and mixtures of enantiomers or diastereomers, are included within the scope of the sulfonylaminocarbonyl derivatives useful in the present invention.

[0099] Some of the compounds useful in the present invention are capable of further forming nontoxic pharmaceutically acceptable acid-addition and/or base salts. All of these forms are within the scope of the compounds useful in the present invention.

[0100] For example, pharmaceutically acceptable acid addition salts of the compounds useful in the present invention include nontoxic salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihyrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinates suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M., et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science,* 1977;66:1-19).

[0101] Acid addition salts of the compounds useful in the present invention that contain a basic functional group are prepared by contacting the free base form of the sulfonylaminocarbonyl derivative with a sufficient amount of the desired acid, which amount is usually 1 molar equivalent, to produce the salt in the conventional manner.

[0102] Pharmaceutically acceptable base salts of the compounds useful in the present invention are formed with metal cations such as, for example, alkali and alkaline earth metal cations, or amines such as, for example, organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge, supra., 1977).

[0103] Base salts of the compounds useful in the present invention that contain an acidic functional group are prepared by contacting the free acid form of the sulfonylaminocarbonyl derivative with a sufficient amount of the desired

base, which amount is usually 1 molar equivalent, to produce the salt in the conventional manner.

[0104] Certain of the compounds useful in the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are encompassed within the scope of the compounds useful in the present invention.

[0105] Examples of sulfonylaminocarbonyl derivatives useful in the present invention are found below. The examples are for illustration purposes, and are not to be construed as limiting the scope of the invention in any respect.

EXAMPLE 1

[0106] Carbamic acid, [[(diphenylmethyl)amino]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 2

[0107] Carbamic acid, [[(diphenylmethyl)amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)phenyl ester

EXAMPLE 3

[0108] Carbamic acid, [[(diphenylmethyl)amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 4

[0109] Carbamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 5

[0110] Carbamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)phenyl ester

EXAMPLE 6

[0111] Carbamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 7

[0112] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[[[2,6-bis(1-methylethyl)phenyl]-amino]sulfonyl]-

EXAMPLE 8

[0113] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(diphenylmethyl)amino]-sulfonyl]-

EXAMPLE 9

[0114] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(2,2-diphenylethyl)amino]-sulfonyl]-

EXAMPLE 10

[0115] Carbamic acid, [[(2,2-diphenylethyl)amino]sulfonyl]-, 2,6-bis(1-methylethyl)-phenyl ester

EXAMPLE 11

[0116] Carbamic acid, [[(2,2-diphenylethyl)amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-phenyl ester

EXAMPLE 12

[0117] Carbamic acid, [[(2,2-diphenylethyl)amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 13

[0118] Carbamic acid, [(phenylamino)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 14

[0119] Carbamic acid, [(phenylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-hydroxyphenyl ester

EXAMPLE 15

[0120] Carbamic acid, [(phenylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-phenyl ester

EXAMPLE 16

[0121] Carbamic acid, [(1H-benzimdazol-2-ylamino)sulfonyl]-, 2,6-bis(1-methylethyl)-phenyl ester

EXAMPLE 17

[0122] N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis(phenylmethyl)amino]-sulfonyl]-urea

EXAMPLE 18

[0123] N-[[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-N'-(diphenylmethyl)-urea

EXAMPLE 19

[0124] N-[2,6-bis(1-methylethyl)phenyl]-N'-[(9H-fluoren-9-ylamino)-sulfonyl]-urea

EXAMPLE 20

[0125] N-[2,6-bis(1-methylethyl)phenyl-N'-[[bis(1-methylethyl)amino]-sulfonyl]-urea

EXAMPLE 21

[0126] N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dibutylamino)sulfonyl]-urea

EXAMPLE 22

[0127] N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(1-methylethyl)-(phenylmethyl)amino]-sulfonyl]-urea

EXAMPLE 23

[0128] N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dioctylamino)sulfonyl]-urea

EXAMPLE 24

[0129] Carbamic acid, [[bis(phenylmethyl)amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-phenyl ester

EXAMPLE 25

[0130] Carbamic acid, [[bis(phenylmethyl)amino]sulfonyl]-, 2,6-bis(1-methylethyl)-phenyl ester

EXAMPLE 26

[0131] Carbamic acid, [(diphenylamino)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 27

[0132] Carbamic acid, [(dibutylamino)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 28

[0133] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 29

[0134] N'-[[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-N,N-bis(phenylmethyl)-urea

EXAMPLE 30

[0135] Carbamic acid, [(dibutylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 31

[0136] Carbamic acid, [(dipentylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 32

[0137] Carbamic acid, [[bis(1-methylethyl)amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 33

[0138] Carbamic acid, [(dihexylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 34

[0139] Carbamic acid, [(hexylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 35

[0140] N-[2,6-bis(1-methylethyl)phenyl]-N'-[(4-phenyl- 1-piperidinyl)-sulfonyl]-urea

EXAMPLE 36

[0141] N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dihexylamino)sulfonyl]-urea

EXAMPLE 37

[0142] N-[[bis[3-(dimethylamino)propyl]amino]sulfonyl]-N'-[2,6-bis(1-methylethyl)phenyl] -urea

EXAMPLE 38

[0143] Carbamic acid, [[methyl(2-phenylethyl)amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 39

[0144] N-[2,6-bis(1-methylethyl)phenyl]-N'-[(hexylamino)sulfonyl]-urea

EXAMPLE 40

[0145] Carbamic acid, [[bis[3-(dimethylamino)propyl]amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 41

[0146] N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis[(tetrahydro-2-furanyl)methyl]amino]sulfonyl]-urea, (=+/)-

EXAMPLE 42

[0147] Carbamic acid, [[methyl[2-(2-pyridinyl)ethyl]amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester, monohydrochloride

EXAMPLE 43

[0148] Carbamic acid, [(methyloctylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 44

[0149] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(diethylamino)sulfonyl]-

EXAMPLE 45

[0150] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(methyloctylamino)sulfonyl]-

EXAMPLE 46

[0151] Carbamic acid, [(dioctylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 47

[0152] Carbamic acid, [[(2,2-diphenylethyl)amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methoxyphenyl ester

EXAMPLE 48

[0153] Carbamic acid, (phenoxysulfonyl)-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 49

[0154] Carbamic acid, [(hexyloxy)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 50

[0155] Carbamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methoxyphenyl ester

EXAMPLE 51

[0156] Carbamic acid, [(dodecyloxy)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 52

[0157] Carbamic acid, [(didecylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 53

[0158] Carbamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-, dodecyl ester

EXAMPLE 54

[0159] Carbamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-, methyl ester

EXAMPLE 55

[0160] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, dodecyl ester

EXAMPLE 56

[0161] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, methyl ester

EXAMPLE 57

[0162] Carbamic acid, [(hexyloxy)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 58

[0163] Carbamic acid, (4-morpholinylsulfonyl)-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 59

[0164] Carbamic acid, (1-piperidinylsulfonyl)-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 60

[0165] Sulfamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]-, octadecyl ester

EXAMPLE 61

[0166] Carbamic acid, [(dodecyloxy)sulfonyl]-, dodecyl ester

EXAMPLE 62

[0167] Carbamic acid, [[bis(1-methylethyl)amino]sulfonyl]-, 2,6-bis(1-methylethyl)-phenyl ester

EXAMPLE 63

[0168] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[[cyclohexyl(1-methylethyl)amino]-sulfonyl]-

EXAMPLE 64

[0169] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dipentylamino)sulfonyl]-

EXAMPLE 65

[0170] Carbamic acid, [[(1-methylethyl)phenylmethyl)amino]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 66

[0171] Carbamic acid, (1-pyrrolidinylsulfonyl)-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 67

[0172] Carbamic acid, [(hexylamino)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 68

[0173] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis(2-methylpropyl)amino]-sulfonyl]-

EXAMPLE 69

[0174] Sulfamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]-, dodecyl ester

EXAMPLE 70

[0175] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-pyrrolidinylsulfonyl)-

EXAMPLE 71

[0176] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-piperidinylsulfonyl)-

EXAMPLE 72

[0177] Carbamic acid, [(2,3-dihydro-1H-indol-1-yl)sulfonyl]-, 2,6-bis(1-methylethyl)-phenyl ester

EXAMPLE 73

[0178] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[[ethyl(2-propenyl)amino]-sulfonyl]-

EXAMPLE 74

[0179] Urea, N-[[bis(3-methylbutyl)amino]sulfonyl]-N'-[2,6-bis(1-methylethyl) phenyl]-

EXAMPLE 75

[0180] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(didecylamino)sulfonyl]-

EXAMPLE 76

[0181] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(didodecylamino)sulfonyl]-

EXAMPLE 77

[0182] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dipropylamino)sulfonyl]-

EXAMPLE 78

[0183] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dicyclohexylamino)-sulfonyl]-

EXAMPLE 79

[0184] Carbamic acid, [[(2,4,6-trimethoxyphenyl)amino]sulfonyl]-, dodecyl ester

EXAMPLE 80

[0185] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(methyloctadecylamino)-sulfonyl]-

EXAMPLE 81

[0186] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(di-2-propenylamino)-sulfonyl]-

EXAMPLE 82

[0187] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(1,1-dimethylethyl)(1-methylethyl)-amino]sulfonyl]-

EXAMPLE 83

[0188] Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis(1-methylpropyl)-amino]-sulfonyl]-

EXAMPLE 84

[0189] Urea, N-[2,6-bis(1-methylethyl)phenyl)-N'-[(methyltetradecylamino)-sulfonyl]-

EXAMPLE 85

[0190] Carbamic acid, [(dioctylamino)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 86

[0191] Carbamic acid, [[cyclohexyl(1-methylethyl)amino]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 87

[0192] Carbamic acid, [(methyloctylamino)sulfonyl]-, 2,6-bis(1-methylethyl)-phenyl ester

EXAMPLE 88

[0193] Carbamic acid, [(dihexylamino)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 89

[0194] Carbamic acid, [(dipentylamino)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 90

[0195] Sulfamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]-, decyl ester

EXAMPLE 91

[0196] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)phenyl ester

EXAMPLE 92

[0197] Carbamic acid, [(dodecyloxy)sulfonyl]-, [1,1':3',1"-terphenyl]-2'-yl ester

EXAMPLE 93

[0198] Carbamothioic acid, [(dodecyloxy)sulfonyl]-, S-[2,6-bis(1-methylethyl)-phenyl] ester

EXAMPLE 94

[0199] Sulfamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]-, 1-methylheptyl ester, (=+/)-

EXAMPLE 95

[0200] Sulfamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 96

[0201] Carbamic acid, [[(diphenylmethyl)amino]sulfonyl]methyl-, 2,6-bis(1,1-dimethylethyl)phenyl ester

EXAMPLE 97

[0202] Carbamic acid, (phenoxysulfonyl)-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 98

[0203] Carbamic acid, [(2,6-dimethylphenoxy)sulfonyl]-, 2,6-bis(1-methylethyl)-phenyl ester

EXAMPLE 99

[0204] Urea, N'-[2,6-bis(1-methylethyl)phenyl]-N-[(dibutylamino)sulfonyl]-N-methyl-

EXAMPLE 100

[0205] Carbamic acid, [[2,6-bis(1,1-dimethylethyl)phenoxy]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)phenyl ester

EXAMPLE 101

[0206] DL-Tryptophan,]a/-methyl-N-[[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-carbonyl]amino]sulfonyl]-, methyl ester

EXAMPLE 102

[0207] Carbamic acid, [[2,6-bis(1,1-dimethylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 103

[0208] Carbamic acid, [(2,6-difluorophenoxy)sulfonyl]-, 2,6-bis(1-methylethyl)-phenyl ester

EXAMPLE 104

[0209] Urea, N-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N'-[[(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]sulfonyl]-, (4S-#cis/)-

EXAMPLE 105

[0210] Urea, N-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N'-[[(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)amino]sulfonyl]-, stereoisomer

EXAMPLE 106

[0211] Sulfamic acid, (1-oxodecyl)-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 107

[0212] Carbamic acid, [(hexadecyloxy)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 108

[0213] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-dimethoxyphenyl ester

EXAMPLE 109

[0214] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 1-methylheptyl ester

EXAMPLE 110

[0215] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)-4-nitrophenyl ester

EXAMPLE 111

[0216] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 1,2-ethanediyl ester

EXAMPLE 112

[0217] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 1,2,3-propanetriyl ester

EXAMPLE 113

[0218] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-bromo-2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 114

[0219] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, [1,1':3',1"-terphenyl]-2'-yl ester

EXAMPLE 115

[0220] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methoxyphenyl ester

EXAMPLE 116

[0221] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-fluoro-2,3,5,6-tetrakis(1-methylethyl)phenyl ester

EXAMPLE 117

[0222] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-chloro-2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 118

[0223] Stigmasta-5,22-dien-3-ol, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-carbamate, (3α)-

EXAMPLE 119

[0224] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester

EXAMPLE 120

[0225] Sulfamic acid, [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 121

[0226] Stigmastan-3-ol, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-carbamate, (3α)-

EXAMPLE 122

[0227] Sulfamic acid, [[2,6-bis(1-methylethyl)phenyl]acetyl]-, 2,6-bis(1-methylethyl)-phenyl ester

EXAMPLE 123

[0228] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-methoxy-2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 124

[0229] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4,6-tris(1-methylethyl)phenyl ester

EXAMPLE 125

[0230] Carbamic acid, [[2,4,6-tris(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 126

[0231] Carbamic acid, [[2,4,6-tris(1-methylethyl)phenoxy]sulfonyl]-,2,4,6-tris(1-methylethyl)phenyl ester

EXAMPLE 127

[0232] Carbamic acid, [[2,4,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4,6-tris(1,1-dimethylethyl)phenyl ester

EXAMPLE 128

[0233] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl] dithio]-2,6-bis(1,1-dimethylethyl)phenyl ester

EXAMPLE 129

[0234] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4-bis(1-methylethyl)phenyl ester

EXAMPLE 130

[0235] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-[(dimethylamino)-methyl]-2,6-bis(1-methylethyl) phenyl ester

EXAMPLE 131

[0236] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, tricyclo[3.3.1.1^{3,7}]-dec-2-yl ester

EXAMPLE 132

[0237] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-hydroxy-2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 133

[0238] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, cyclohexyl ester

EXAMPLE 134

[0239] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 3,3',5,5'-tetrakis(1-methylethyl)[1,1'-biphenyl]-4,4'-diyl ester

EXAMPLE 135

[0240] Carbamic acid, [[4-hydroxy-2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 136

[0241] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, tricyclo[3.3.1.1^{3,7}]-dec-1-yl ester

EXAMPLE 137

[0242] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2-(1,1-dimethylethyl)-6-methylphenyl ester

EXAMPLE 138

[0243] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 5-methyl-2-(1-methylethyl)cyclohexyl ester

EXAMPLE 139

[0244] Carbamothioic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, *S*-[2,6-bis(1-methylethyl)phenyl] ester

EXAMPLE 140

[0245] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, (2,6-diethylphenyl)methyl ester

EXAMPLE 141

[0246] Carbamic acid, sulfonylbis-, bis[2,6-bis(1-methylethyl)phenyl] ester

EXAMPLE 142

[0247] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, (2*S*,6*S*)-2,6-bis(1-methylethyl)cyclohexyl ester

EXAMPLE 143

[0248] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-(1,1-dimethylethyl)-2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 144

[0249] (2-Phenyl-cyclopropanecarbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 145

[0250] [(2,5-Dimethoxy-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 146

[0251] [(2,4,6-Trimethyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 147

[0252] [(2,4,6-Trimethoxy-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 148

[0253] (Thiophen-2-yl-acetyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 149

[0254] (Thiophen-3-yl-acetyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 150

[0255] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-fluorophenyl ester

EXAMPLE 151

[0256] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4-difluorophenyl ester

EXAMPLE 152

[0257] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, pentafluorophenyl ester

EXAMPLE 153

[0258] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-difluorophenyl ester

EXAMPLE 154

[0259] Acetic acid 2-(2,6-diisopropyl-phenoxysulfonylamino)-2-oxo-1-(2,4,6-triisopropyl-phenyl)-ethyl ester

EXAMPLE 155

[0260] Cyclohexylacetyl-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 156

[0261] [(2-Methoxy-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 157

[0262] (Oxo-phenyl-acetyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 158

[0263] [(2-Trifluoromethyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 159

[0264] (2-Phenyl-propionyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 160

[0265] Diphenylacetyl-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 161

[0266] (Cyclopentyl-phenyl-acetyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 162

[0267] [Hydroxy-(2,4,6-triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 163

[0268] Triphenylacetyl-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 164

[0269] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, (2*R*,6*S*)-2,6-bis(1-methylethyl)cyclohexyl ester

EXAMPLE 165

[0270] (1,2,3,4-Tetrahydro-naphthalene-2-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 166

[0271] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,3,5,6-tetramethylphenyl ester

EXAMPLE 167

[0272] (3-Methyl-2-phenyl-pentanoyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 168

[0273] (1-Phenyl-cyclopentanecarbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 169

[0274] (2-Phenyl-butyryl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 170

[0275] (Cyclohexyl-phenyl-acetyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 171

[0276] (2,2-Diphenyl-propionyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 172

[0277] [Bis-(4-chloro-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 173

[0278] (9H-Xanthene-9-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 174

[0279] (9H-Fluorene-9-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 175

[0280] (Bromo-phenyl-acetyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 176

[0281] (3-Phenyl-propionyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 177

[0282] Sulfamic acid, [[[2,4,6-tris(1-methylethyl)phenyl]amino]carbonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 178

[0283] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 3-pyridinyl ester

EXAMPLE 179

[0284] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-dimethylphenyl ester

EXAMPLE 180

[0285] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-hydroxy-2,6-diisopropylphenyl ester

EXAMPLE 181

[0286] Methyl-[(2,4,6-triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 182

[0287] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-nitro-phenyl ester

EXAMPLE 183

[0288] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-acetyl-2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 184

[0289] Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-fluoro-2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 185

[0290] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-fluoro-2,6-diisopropylphenyl ester

EXAMPLE 186

[0291] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-dimethoxy-phenyl ester

EXAMPLE 187

[0292] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-amino-2,6-diisopropylphenyl ester

EXAMPLE 188

[0293] 6-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenyl)-hexanoic acid ethyl ester

EXAMPLE 189

[0294] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,4,6-trimethoxy-phenyl ester

EXAMPLE 190

[0295] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-tert-butyl-2,6-diisopropylphenyl ester

EXAMPLE 191

[0296] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-acetyl-2-isopropyl-phenyl ester

EXAMPLE 192

[0297] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-methoxyphenyl ester

EXAMPLE 193

[0298] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-dichloro-phenyl ester

EXAMPLE 194

[0299] 3-[3-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]-sulfamoyloxy}-phenyl)-ureido]-propionic acid ethyl ester

EXAMPLE 195

[0300] [5-tert-Butoxycarbonylamino-5-(3,5-diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenyl-carbamoyl)-pentyl]-carbamic acid tert-butyl ester

EXAMPLE 196

[0301] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-acetylamino-2,6-diisopropylphenyl ester

EXAMPLE 197

[0302] [2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2,6-diaminohexanoylamino)-2,6-diisopropyl-phenyl ester; compound with generic inorganic neutral component

EXAMPLE 198

[0303] [(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenylcarbamoyl)-methyl]-carbamic acid tert-butyl ester

EXAMPLE 199

[0304] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid dodecyl ester

EXAMPLE 200

[0305] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-acetylamino)-2,6-diisopropyl-phenyl ester

EXAMPLE 201

[0306] [2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-4-methylsulfanyl-butyrylamino)-2,6-diisopropyl-phenyl ester

EXAMPLE 202

[0307] {[4-(1-Hydroxy-1-methyl-ethyl)-2,6-diisopropyl-phenyl]-acetyl}-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 203

[0308] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-bromo-2,6-diisopropylphenyl ester

EXAMPLE 204

[0309] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[2-amino-3-(1H-indol-3-yl)-propionylamino]-2,6-diisopropyl-phenyl ester

EXAMPLE 205

[0310] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-dimethylamino-propoxy)-2,6-diisopropyl-phenyl ester

EXAMPLE 206

[0311] [2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((R)-2-amino-propionylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid

EXAMPLE 207

[0312] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-2-methylpropionylamino)-2,6-diisopropyl-phenyl ester

EXAMPLE 208

[0313] [2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-amino-propoxy)-2,6-diisopropyl-phenyl ester

EXAMPLE 209

[0314] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-thiocyanatophenyl ester

EXAMPLE 210

[0315] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-methylphenyl ester

EXAMPLE 211

[0316] [1-(4-Dimethylamino-phenyl)-cyclopentanecarbonyl]-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 212

[0317] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-cyano-2,6-diisopropylphenyl ester

EXAMPLE 213

[0318] [1-(4-Nitro-phenyl)-cyclopentanecarbonyl]-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 214

[0319] [1-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenylcarbamoyl)-3-methylsulfanyl-propyl]-carbamic acid tert-butyl ester

EXAMPLE 215

[0320] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[3-(2,6-diisopropyl-phenyl)-ureido]-2,6-diisopropyl-phenyl ester

EXAMPLE 216

[0321] [2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-4-methylpentanoylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid

EXAMPLE 217

[0322] Sulfamic acid, [[[[1-[4-(dimethylamino)phenyl]cyclopenty]methyl]-amino]carbonyl]- 2,6-bis(1-methylethyl) phenyl ester

EXAMPLE 218

[0323] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(3-phenylureido)-phenyl ester

EXAMPLE 219

[0324] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-tert-butyl-ureido)-2,6-diisopropyl-phenyl ester

EXAMPLE 220

[0325] [2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-amino-propionylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid

EXAMPLE 221

[0326] Carbamic acid, [[[2-(phenylmethyl)phenyl]amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)phenyl ester

EXAMPLE 222

[0327] (2,3-Dihydro-indole-1-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 223

[0328] Sulfamic acid, [[(triphenylmethyl)amino]carbonyl]-, 2,6-bis(1-methylethyl)phenyl ester

EXAMPLE 224

[0329] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-cyano-vinyl)-2,6-diisopropyl-phenyl ester

EXAMPLE 225

[0330] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(thiophene-2-sulfonylamino)-phenyl ester

EXAMPLE 226

[0331] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(5-dimethylaminonaphthalene-1-sulfonylamino)-2,6-diisopropyl-phenyl ester

EXAMPLE 227

[0332] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-methanesulfonylamino-phenyl ester

EXAMPLE 228

[0333] 3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-benzoic acid methyl ester

EXAMPLE 229

[0334] [2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(benzylamino-methyl)-2,6-diisopropyl-phenyl ester; compound with generic inorganic neutral component

EXAMPLE 230

[0335] [2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-3-hydroxypropionylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid

EXAMPLE 231

[0336] [2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-4-carbamoylbutyrylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid

EXAMPLE 232

[0337] [2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-3-methylbutyrylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid

EXAMPLE 233

[0338] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-hydroxymethyl-2,6-diisopropyl-phenyl ester

EXAMPLE 234

[0339] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-carbamoyl-2,6-diisopropylphenyl ester

EXAMPLE 235

[0340] [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[3-(3,5-dichloro-phenyl)-thioureido]-2,6-diisopropyl-phenyl ester

EXAMPLE 236

[0341] ((E)-2-Methyl-3-phenyl-acryloyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 237

[0342] (2-Oxo-2H-chromene-3-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester

EXAMPLE 238

[0343] N-[2,6-bis(1-methylethyl)phenyl]-N'-(hexadecylsulfonyl)-urea

EXAMPLE 239

[0344] N-[2,6-bis(1-methylethyl)phenyl]-N'-[(6-ethoxy-2-benzothiazolyl)sulfonyl]-urea

EXAMPLE 240

[0345] N-[2,6-bis(1-methylethyl)phenyl]-N'-(tetradecylsulfonyl)-urea

EXAMPLE 241

[0346] N'-[2,6-bis(1-methylethyl)phenyl]-N-methyl-N-(tetradecylsulfonyl)-urea

EXAMPLE 242

[0347] N-[2,6-bis(1-methylethyl)phenyl]-N'-(tridecylsulfonyl)urea

EXAMPLE 243

[0348] N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-phenyl-1-nonylsulfonyl)urea

EXAMPLE 244

[0349] N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-decylsulfonyl)urea

EXAMPLE 245

[0350] N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-phenyl-1-tetradecylsulfonyl)urea

EXAMPLE 246

[0351] N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-octadecylsulfonyl)urea

EXAMPLE 247

[0352] N-[2,4,6-trimethoxyphenyl]-N'-(2-octadecylsulfonyl)urea

EXAMPLE 248

[0353] N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-methyl-2-pentadecylsulfonyl)urea

EXAMPLE 249

[0354] N-[2,4,6-trimethoxyphenyl]-N'-(2-methyl-2-pentadecylsulfonyl)urea

EXAMPLE 250

[0355] Carbamic acid, [[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-, dodecyl ester

[0356] Sulfonylaminocarbonyl derivatives useful in the present invention may be identified using the methods described below.

BIOLOGICAL METHODS

[0357] Introduction: Described below is an in vitro, cell-based, high throughput screening assay that reliably identifies inhibitors of NF-κB mediated transcription. While the assay described below utilized inhibitors which were sulfonylaminocarbonyl derivatives useful in the present invention, the assay may be used to screen for any inhibitor of NF-κB mediated transcription.

[0358] The assay takes advantage of AURORA (Aurora Bioscience Corporation, La Jolla, California) fluorescence technology. Endothelial cell vein-304 (ECV-304) cells, an endothelial-like immortalized cell type, may be stably transfected with a plasmid vector containing the cDNA for the enzyme β-lactamase (under the control of a basal promoter, Stratagene pNFκB-luc vector) and 5 copies of an human immunodeficiency virus-1 (HIV-1) NF-κB binding site. ECV-304 cells are described by Takahashi K. et al. in Spontaneous Transformation and Immobilization of Human Endothelial Cells, *In Vitro Cell. Dev. Biol.* 1990;25:265-274. Activation of NF-κB in ECV-304 by cytokines such as TNF-α or interleuken- 1 beta (IL-1β) results in the production of β-lactamase, which cleaves a green fluorescent substrate (excitation/emission wavelengths 395 nm/530 nm) to yield a blue fluorescent product (excitation/emission wavelengths 395 nm/460 nm). Visually, the uncleaved green fluorescent substrate is sequestered intracellularly and emits green fluorescence, while the cleaved product emits blue fluorescence. Fluorescence is quantitated spectrophotometrically, and the spectral intensity of blue fluorescence versus green fluorescence can be used to calculate the degree of activation of NF-κB.

[0359] The assay was performed as outlined here and described in detail below. ECV-304 cells permanently transfected with the NF-κB driven (β-lactamase gene (ECV-304 NF-κB.βlaZ) were plated in clear-bottom, black 96-well plates (1.25×10^4 cells/well) in media-199 (M-199) media containing 2% fetal bovine serum (FBS). Approximately 18 hours later the cells were stimulated with either 10 ng/mL of TNF-α or 100 pg/mL of IL-1β, and incubated for 6 hours at 37°C in the presence or absence of a compound useful in the present invention. The AURORA fluorescent disclosing reagent was then added. After one additional hour, the plates were read in a fluorometer at the blue 395 nm/460 nm (excitation/emission) and green 395 nm/530 nm wavelengths. Then the blue/green emission ratio was calculated. Percent inhibition was calculated by comparing fluorescence in the presence of a sulfonylaminocarbonyl derivative useful in the present invention with fluorescence in the absence of said sulfonylaminocarbonyl derivative under conditions of maximum stimulation with TNF-α or IL-1β. An IC_{50} for said sulfonylaminocarbonyl derivative was determined from a dose-response curve. This assay was designed to be optionally run in either high or low throughput screening modes.

[0360] Materials: ECV-304 cells were obtained from American Type Culture Collection (ATCC). Cytokines TNF-α and IL-1β were obtained from R&D Systems. Lipofectamine, M199, and penicillin/streptomycin 1000 U (P/S) were from GIBCO-BRL. Reagents A, B, and C are proprietary reagents from Aurora Technologies. The FBS is from Summit Technologies. The CCF2 dye was from Aurora Biosciences, La Jolla, California.

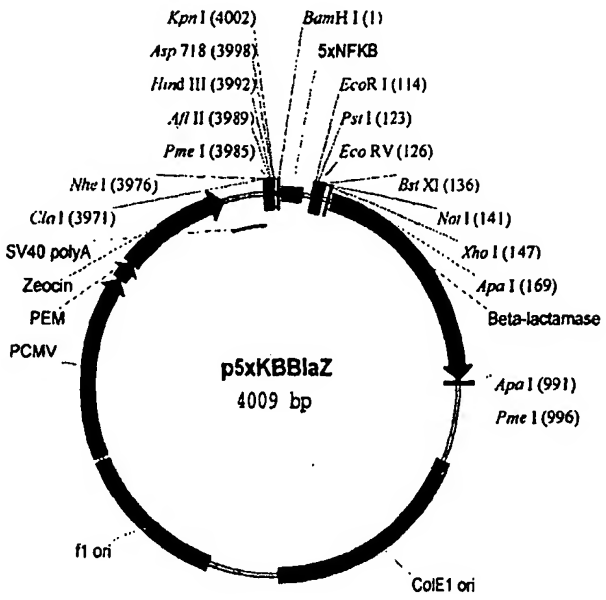
Methods:

(i) ECV-304 NF-κB.βlaZ Cell Line:

[0361] Five copies of the HIV-1 NF-κB binding site (5'-TGGGGACTTTCCGC-3') along with a TATA box were inserted into the EcorRI/BamHI sites of plasmid pMCRBlaZ to create plasmid p5xKBBlaZ, which procedure is illustrated in Scheme 1 below.

Scheme 1

Five copies of the HIV-1 NF-κB binding site
+ TATA box
+ plasmid pMCRBlaZ ⟶



Plasmid p5xKBBlaZ

[0362] The parental plasmid, pMCRBlaZ, contains a multiple cloning site upstream of the β-lactamase gene as well as a Zeocin antibiotic resistance gene.

[0363] Plasmid p5xKBBlaZ was transfected into ECV-304 cells using lipofectamine and the well-known standard conditions found on the package insert. Cells were selected for antibiotic resistance with Zeocin for approximately 2 weeks. After the stable population had been expanded to a significant number of cells, it was stimulated with IL-1β and stained with AURORA CCF2 dye, a membrane permeant, intracellularly-trapped, fluorescent substrate. Cells that fluoresced blue (indicating a positive response of the NF-κB/β-lactamase reporter to stimulation by IL-1β) in the stimulated/stained population were then sorted by flow cytometry into a pool. The pool was expanded and stained with CCF2, and then the cells that fluoresced green from this unstimulated population (indicating a low background of the NF-κB/β-lactamase reporter construct) were cloned by flow cytometry after adding 1 cell per well in 96-well plates. Clones were allowed to expand. Each cloned cell line was then examined for fold stimulation after stimulation with IL-1β using a CCF2 reporter assay, and these stimulated cells were compared to unstimulated cells. The cloned cell line with the maximal fold induction (plate 1, row E, cell 8 or 1E8) was chosen for further assay development. This clone consistently showed the highest fluorescence signal to noise ratio upon stimulation with TNF-α or IL-1β.

(ii) Assay Development:

[0364] The assay described herein was initially developed for high throughput screening purposes. As such, several factors were taken into consideration in the process. The assay was developed to minimize handling (i.e., no media changes, washes, etc.). Conditions were established to optimize the incubation period to 4 to 6 hours for logistical reasons. The assay was also optimized to its ability to tolerate the presence or absence of serum and the concentration of dimethylsulfoxide (DMSO) that could be used without interference of the fluorescence generated from the activation

of NF-κB. Cytokine stability and optimal cell density were also optimized. Also, no difference in NF-κB stimulation in ECV-304 cells separated in lineage by 20 passages (Passages 5 and 25) was found.

(iii) Regeants:

[0365]

Cells: ECV-304 NF-κB β-Lactamase clone 1E8
Complete Media: M199, 10%FBS (nonheat inactivated), 1% P/S, 200 μg/mL Zeocin;
Assay Media: M199, 2% FBS, no antibiotics
Cell Culture: 0.5 × 106 cells/T 150 culture flask, 30 mL complete media, fed every other day; harvested Day 7, approximate yield 1.1 (107/flask)
Assay Seeding Density: 1.78 × 105/mL, 70 μL/well—96-well plate, (12,500 cells/well)
Quality Controls: The proteosome inhibitors MG132, MG262, and clastolactacystine β-lactone may be used, as these agents irreversibly inhibit the proteasomal breakdown of IkB (McCormicack, et al., *Journal of Biological Chemistry,* 1997;272(42):26103-26109 and Craui et al., *Journal of Biological Chemistry,* 1997;272(20): 13437-13445.)
Inhibitors: Prepared stock solutions of aminosulfonyl derivatives at 10 mM concentration in DMSO;
Diluted stock solutions in 96-well diluting plate as follows:

a) Added 20 μL of stock solution into 180 μL of M199 = A,
b) Added 20 μL A into 180 μL M199 = B,
c) Added 10 μL of B into appropriate well in assay plate (the final concentration of drug is 10 μM), and
(d) Diluted further for IC_{50} determinations.

Activation Cytokines TNF-α and IL-1β:

Stock solution of TNF-α: R&D Systems 210-TA, 10 μg was diluted into 2 mL of phosphate buffered saline (PBS) containing 0.1% bovine serum albumin (BSA) (concentration of TNF-α = 5 μg/mL);
Diluted TNF-α stock solution 1:100: 90 μL of TNF-α stock solution was diluted into 9.0 mL of M199 media (concentration of TNF-α = 50 ng/mL); and
Added 20 μL of the solution of TNF-α at 50 ng/mL to all wells except reagent control wells, and cell control wells (final concentration of TNF-α in well = 10 ng/mL).
Stock solution of IL-1β: R&D Systems 203-LB, 5 μg was diluted into 1 mL of PBS containing 0.1% BSA (concentration of IL-1β= 5 μg/mL);
Diluted the IL-1β stock solution 1:1000: 20 μL of IL-1β stock solution was diluted into 20 mL of M199 (concentration of IL-1β = 5 ng/mL);
Diluted the 5 ng/mL solution of IL-1β 1:10: 0.5 mL of the 5 ng/mL solution IL-1β at a concentration of 5 ng/mL was diluted into 5.0 mL of M199 (concentration of IL-1β = 500 pg/mL); and
Added 20 μL the solution of the 500 pg/mL IL-1β at to all wells except reagent control wells and cell control wells (final concentration IL-1β in well = 100 pg/mL).

(iv) A High Throughput Screening Assay Procedure:

[0366]

Table 1.

Plate Map												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
A	USC	T	O	O	O	O	O	O	O	O	O	B
B	USC	T	O	O	O	O	O	O	O	O	O	B
C	USC	T	O	O	O	O	O	O	O	O	O	B
D	USC	T	O	O	O	O	O	O	O	O	O	B
E	USC	T	O	O	O	O	O	O	O	O	O	B
F	USC	T	O	O	O	O	O	O	O	O	O	B
G	USC	MG	O	O	O	O	O	O	O	O	O	B

Table 1. (continued)

Plate Map												
	1	2	3	4	5	6	7	8	9	10	11	12
H	USC	MG	O	O	O	O	O	O	O	O	O	B

Column 1 = **USC**, Unstimulated cell control wells.

Column 2 A-F = **T**, Maximal activation control wells.

Column 2 G-H = **MG**, MG132 quality control.

Column 12 = **B**, Reagent background wells.

Columns 3-11 = **O**, Sulfonylaminocarbonyl derivatives in triplicate at a concentration of 10 μM (for screening purposes) or at varying concentrations for dose response studies (IC_{50}).

[0367] Plates for the HTS are configured in an alternative format.

[0368] PM Day 1: Seeded cells at 0.178 × 10^6/mL, 70 μL/well, in assay media AM Day 2:

a) DMSO Control: Added 10 μL of a 1% DMSO solution in M199 to the following wells (final concentration of DMSO in well = 0.1%): Added to B wells (reagent control: assay media, no cytokine, no cells), USC wells (unstimulated cell control: cells, assay media, no activation cytokine), and T wells (maximal activity: cells, assay media, cytokine);

b) Inhibitor: Added 10 μL of a sulfonylaminocarbonyl derivative at 10× desired final concentration to the following wells: Added to all O wells (unknowns: cells, assay media, cytokine) and MG wells (quality control: cells, assay media, cytokine). No inhibitor should be added to USC wells, B wells, or T wells.

c) Activation Cytokine: Added 20 μL of the 50 ng/mL solution of TNF-α (to give a 10 ng/mL final concentration of TNF-α) or 20 μL of the 500 pg/mL solution of IL-1β (to give a 100 pg/mL final concentration of IL-1β) to all T wells, O wells, and MG wells. No cytokine was added to USC wells or B wells.

d) Incubation after stimulation of cells with an activation cytokine, with or without a sulfonylaminocarbonyl derivative: 6 hours, 37°C, 5% CO_2 atmosphere

e) Preparation of AURORA CCF2 Fluorescence Disclosing Substrate Solutions:

[0369] Prepared four separate solutions of 2 mL each for each plate using the amounts recited in Table 2 below according to the following procedure.

[0370] Added Reagent A to 50-mL tube first, then added Reagent B. Mixed. Then added Reagent C. Mixed.

Table 2.

Substrate Formulation Instructions		
(Reagent A + Reagent B)		+ Reagent C
6 μL	60 μL	1 mL
24 μL	240 μL	4 mL
48 μL	480 μL	8 mL
60 μL	600 μL	10 mL
2 mL/plate, 20 μL/well; make 2 mL extra		

[0371] Incubation after addition of the AURORA CCF2 fluorescence disclosing solution: 1 hour at room temperature in the dark

[0372] Spectrophotometric analysis: CYTOFLUOR (Millipore Corporation, Bedford, Massachusetts) 2 instruments using the following wavelengths in nanometers. Excite 395 Emit 460 (Blue) and Excite 395 Emit 530 (Green)

(v) Calculation of Data

[0373]

BKG Blue (BB) = Average reagent background blue emission.

BKG Green (BG) = Average reagent background green emission.

Corrected Blue (CB)	= Subtract BB from all blue readings on plate.
Corrected Green (CG) =	Subtract BG from all green readings on plate.
Blue/Green Ratio (BGR) =	Divide CB by CG (CB/CG).
BGRF =	Divide BGR by BGR of USC wells.
Maximum Activity =	Average of BGRF of stimulated cells (TNF-α max or IL-1β max).
% Inhibition of T Maximum Activity =	(100 - (average BGRF of unknown (cells + inhibitor)/TNF-α max or IL-β max) × 100).

[0374] Representative sulfonylaminocarbonyl derivatives useful in the present invention were tested at a concentration of 10 μM for the ability to inhibit NF-κB mediated transcription using the method described above, and the results are shown below in Table 3 in the column labeled "Percent inhibition at 10 μM."

Table 3.

Inhibition of NF-κB Mediated Transcription (Page 1 of 9)	
Example No.	Percent Inhibition at 10 μM
1	24.83
2	37.20
3	79.34
4	35.32
5	56.40
6	64.92
7	37.04
8	<10[a]
9	33.15
10	39.74
11	50.11
12	57.02
13	<10
14	13.84
15	12.56
16	<10
17	43.76
18	35.92
19	20.24
20	<10
21	29.41
22	20.17
23	38.67
24	30.97
25	33.24
26	32.80
27	26.15
28	30.20
29	38.49
30	52.05
31	74.02

[a] "<10" means percent inhibition was >0 μm, but < 10 μm.

Table 3. (continued)

Inhibition of NF-κB Mediated Transcription (Page 1 of 9)	
Example No.	Percent Inhibition at 10 μM
32	20.33
33	58.63
34	24.30
35	<10
36	51.23
37	<10
38	31.49
39	<10
40	<10
41	<10
42	<10
43	70.23
44	<10
45	53.50
46	34.79
47	41.89
48	13.77
49	22.93
50	39.06
51	47.24
52	<10
53	61.31
54	<10
55	55.07
56	<10
57	20.38
58	<10
59	<10
60	<10
61	27.45
62	<10
63	23.03
64	55.44
65	16.44
66	<10
67	13.82
68	34.32
69	75.49
70	<10
71	<10
72	14.11
73	<10
74	37.58
75	<10
76	<10
77	<10
78	40.90
79	<10

Table 3. (continued)

Inhibition of NF-κB Mediated Transcription (Page 1 of 9)	
Example No.	Percent Inhibition at 10 μM
80	<10
81	<10
82	<10
83	10.58
84	44.82
85	44.99
86	16.00
87	<10
88	<10
89	31.94
90	13.55
91	39.69
92	<10
93	14.51
94	<10
95	33.07
96	10.70
97	<10
98	<10
99	<10
100	50.03
101	<10
102	20.58
103	<10
104	<10
105	<10
106	72.28
107	<10
108	<10
109	51.35
110	15.48
111	<10
112	<10
113	<10
114	<10
115	38.99
116	<10
117	<10
118	<10
119	56.56
120	54.98
121	<10
122	65.26
123	<10
124	11.32
125	11.04
126	10.02
127	74.01

Table 3. (continued)

Inhibition of NF-κB Mediated Transcription (Page 1 of 9)	
Example No.	Percent Inhibition at 10 μM
128	<10
129	<10
130	<10
131	33.39
132	<10
133	<10
134	18.39
135	<10
136	<10
137	<10
138	66.16
139	65.52
140	38.70
141	<10
142	53.87
143	65.81
144	16.19
145	<10
146	28.31
147	<10
148	<10
149	<10
150	<10
151	<10
152	<10
153	<10
154	77.73
155	<10
156	<10
157	<10
158	25.90
159	10.14
160	34.22
161	51.45
162	75.35
163	62.44
164	55.18
165	28.67
166	<10
167	40.01
168	39.14
169	21.31
170	78.57
171	62.23
172	86.90
173	36.94
174	32.24
175	<10

Table 3. (continued)

Inhibition of NF-κB Mediated Transcription (Page 1 of 9)	
Example No.	Percent Inhibition at 10 μM
176	<10
177	63.60
178	<10
179	<10
180	91.96
181	<10
182	69.81
183	<10
184	21.20
185	73.94
186	18.83
187	57.76
188	50.76
189	15.06
190	27.56
191	55.66
192	63.94
193	38.28
194	89.85
195	91.77
196	73.11
197	<10
198	75.78
199	50.73
200	72.66
201	87.14
202	25.39
203	52.22
204	70.04
205	11.72
206	47.89
207	60.34
208	22.39
209	56.80
210	52.45
211	24.65
212	60.24
213	19.73
214	71.74
215	74.72
216	65.43
217	37.08
218	<10
219	15.15
220	65.49
221	44.70
222	<10
223	68.21

Table 3. (continued)

Inhibition of NF-κB Mediated Transcription (Page 1 of 9)	
Example No.	Percent Inhibition at 10 μM
224	<10
225	26.39
226	46.34
227	77.28
228	76.08
229	75.79
230	75.15
231	78.10
232	76.92
233	76.94
234	76.65
235	145.92
236	79.42
237	57.13
238	12.0
239	<10
240	10.3
241	<10
242	<10
243	<10
244	<10
245	16.1
246	<10
247	14.8
248	11.4
249	<10
250	<10

[0375] As shown by cell-based assay data, the sulfonylaminocarbonyl derivatives in Table 3 are inhibitors of NF-κB mediated transcription that are able to cross cell membranes and reach a target in a NF-κB signal pathway. Accordingly, the sulfonylaminocarbonyl derivatives are useful in the present invention for treating a disease or a disorder responsive to the inhibition of NF-κB such as, for example, rheumatoid arthritis and osteoarthritis, autoimmune diseases, psoriasis, asthma, cardiovascular diseases such as, for example, atherosclerosis, acute coronary syndromes including myocardial infarction and unstable angina, and congestive heart failure, Alzheimer's disease, multiple sclerosis, cancer, type II diabetes, metabolic syndrome X, and inflammatory bowel disease.

[0376] In carrying out the methods for treating a disease or a disorder responsive to the inhibition of NF-κB of the present invention, sulfonylaminocarbonyl derivatives useful in the present invention may be administered in a number of pharmaceutically acceptable oral and parenteral forms. Thus, the sulfonylaminocarbonyl derivatives can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the sulfonylaminocarbonyl derivatives can be administered by inhalation, for example, intranasally. Additionally, the sulfonylaminocarbonyl derivatives can be administered transdermally. The following dosage forms may comprise as the active component a compound of Formula I or Formula II, or another sulfonylaminocarbonyl derivative useful in the present invention, or a pharmaceutically acceptable salt thereof.

[0377] For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0378] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

[0379] In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0380] The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0381] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted, and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0382] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0383] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

[0384] Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or, synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0385] Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0386] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0387] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg preferably 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

[0388] In therapeutic use as antagonists or as agents for the treatment of diseases, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01-mg to about 10 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

[0389] Examples of pharmaceutical preparations of the sulfonylaminocarbonyl derivatives useful in the present invention are described below. Such preparations can be administered to a patient, including a human, from 1 to 6 times a day for treatment of diseases and disorders responsive to inhibition of NF-κB mediated transcription.

FORMULATION EXAMPLE 1

[0390]

Tablet Formulation:	
Ingredient	Amount (mg)
Compound of Example 199	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	100

[0391] The compound of Example 199, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch

(for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet.

FORMULATION EXAMPLE 2

Coated Tablets:

[0392] The tablets of formulation Example 1 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

FORMULATION EXAMPLE 3

Infection vials:

[0393] The pH of a solution of 500 g of the compound of Example 3 and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the filtrate is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 25 mg of the compound of Example 3.

FORMULATION EXAMPLE 4

Suppositories:

[0394] A mixture of 25 g of the compound of Example 31, 100 g of soya lecithin, and 1400 g of cocoa butter is fused, poured into molds, and allowed to cool. Each suppository contains 25 mg of the compound of Example 31.

FORMULATION EXAMPLE 5

Solution:

[0395] A solution is prepared from 1 g of the compound of Example 55, 9.38 g of $NaH_2PO_4 \cdot 2H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$, and 0.1 g benzalkonium chloride in 940 mL of double-distilled water. The pH of the solution is adjusted to pH 6.8 using 2 M hydrochloric acid. The solution is diluted to 1.0 L with double-distilled water, and sterilized by irradiation. A 25 mL volume of the solution contains 25 mg of the compound of Example 55.

FORMULATION EXAMPLE 6

Ointment:

[0396] 500 mg of the compound of Example 119 is mixed with 99.5 g of petroleum jelly under aseptic conditions. A 5 g portion of the ointment contains 25 mg of the compound of Example 119.

FORMULATION EXAMPLE 7

Capsules:

[0397] 2 kg of the compound of Example 180 are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the invention compound.

FORMULATION EXAMPLE 8

Ampoules:

[0398] A solution of 2.5 kg of the compound of Example 231 is dissolved in 60 L of double-distilled water. The solution is sterile filtered, and the filtrate is filled into ampoules. The ampoules are lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 25 mg of the compound of

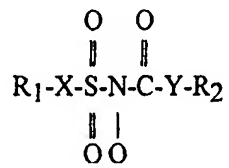
Example 231.

[0399] Having described the methods of the present invention above, embodiments of the present invention are hereupon claimed.

Claims

1. The use of a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment of a disease or a disorder responsive to inhibition of nuclear factor-κB (NF-κB) transcription factors.

2. The use according to Claim 1, wherein the sulfonylaminocarbonyl derivative is a compound of Formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

X and Y are selected from oxygen, sulfur and $(CR'R'')_n$, wherein n is an integer of from 1 to 4 and R' and R" are each independently hydrogen, alkyl, alkoxy, halogen, hydroxy, acyloxy, cycloalkyl, phenyl optionally substituted or R' and R" together form a spirocycloalkyl or a carbonyl;
with the proviso at least one of X and Y is $-(CR'R'')_n-$ and with the further proviso when X and Y are both $(CR'R'')_n$ and R' and R" are hydrogen and n is one, R_1 and R_2 are aryl;
R is hydrogen, a straight or branched alkyl of from 1 to 8 carbon atoms or benzyl;
R_1 and R_2 are each independently selected from:

(a) phenyl or phenoxy each of which is unsubstituted or is substituted with from 1 to 5 substituents selected from:

phenyl,
an alkyl group having from 1 to 6 carbon atoms and which is straight or branched,
an alkoxy group having from 1 to 6 carbon atoms and which is straight or branched;
phenoxy,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl,

- COOH,
- COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched, and
- $(CH_2)_pNR_3R_4$, wherein p is zero or one, and each of R_3 and R_4 is selected from hydrogen or a straight or branched alkyl group having 1 to 4 carbon atoms;

(b) 1- or 2-naphthyl unsubstituted or substituted with from 1 to 3 substituents selected from:

phenyl,
an alkyl group having from 1 to 6 carbon atoms and which is straight or branched,
an alkoxy group having from 1 to 6 carbon atoms and which is straight or branched;
hydroxy,
phenoxy,

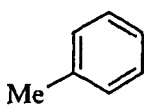
fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl,

- COOH,
- COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched, and
- $(CH_2)_pNR_3R_4$, wherein p, R_3 and R_4 have the meanings defined above;

(c) arylalkyl;
(d) a straight or branched alkyl chain having from 1 to 20 carbon atoms and which is saturated or contains from 1 to 3 double bonds; and
(e) adamantyl or a cycloalkyl group wherein the cycloalkyl moiety has from 3 to 6 carbon atoms;
with the provisos:

(i) where X is $(CH_2)_n$, Y is oxygen, and R_1 is a substituted phenyl, then R_2 is a substituted phenyl;
(ii) where Y is oxygen, X is $(CH_2)_n$, R_2 is phenyl or naphthyl, then R_1 is not a straight or branched alkyl chain; and

(iii) the following compounds are excluded:

X	Y	R	R_1	R_2
CH_2	O	H	$(CH_2)CH_3$	Ph
CH_2	O	H	CH_3	Ph
CH_2	O	H		i-Pr

,

with the further proviso that compounds selected from the group consisting of:

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and
Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)phenyl ester are excluded.

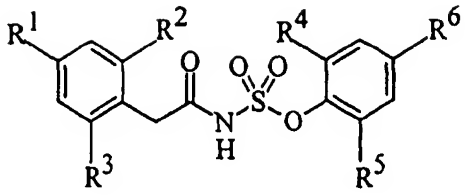
3. The use according to Claim 2, wherein the sulfonylaminocarbonyl derivative is a compound of Formula I, or a pharmaceutically acceptable salt thereof, selected from:

(1,2,3,4-Tetrahydro-naphthalene-2-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester;
[Bis-(4-chloro-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester;
(Bromo-phenyl-acetyl)-sulfamic acid 2,6-diisopropyl-phenyl ester; [(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-hydroxy-2,6-diisopropyl-phenyl ester;
Methyl-[(2,4,6-triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-nitro-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-fluoro-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-dimethoxyphenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-amino-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,4,6-trimethoxy-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-tert-butyl-2,6-diisopropyl-phenyl ester;

[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-acetyl-2-isopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-methoxy-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-dichloro-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid dodecyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-bromo-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-methyl-phenyl ester;
[1-(4-Dimethylamino-phenyl)-cyclopentanecarbonyl]-sulfamic acid 2,6-diisopropyl-phenyl ester;
[1-(4-Nitro-phenyl)-cyclopentanecarbonyl]-sulfamic acid 2,6-diisopropyl-phenyl ester;
3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-benzoic acid methyl ester;
Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl-2,4,6-tris(1-methylethyl)phenyl ester;
Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,4,6-tris(1-methylethyl)phenyl ester;
Sulfamic acid[adamantaneacetyl]-2,6-bis[1-methylethyl)phenyl ester;
Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt;
Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt;
Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester;
Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester; 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]benzeneacetamide;
2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]benzeneacetamide-sodium salt;
2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]carbamate;
2,6-Bis(l -methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]carbamate-sodium salt;
Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester sodium salt;
Sulfamic acid trans-[(2-phenylcyclopropyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (1-oxo-2-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (cyclopentylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (cyclohexylacetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (diphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (triphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [(1-phenylcyclopentyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (1-oxo-2-phenylbutyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (cyclohexylphenyl-acetyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (1-oxo-2,2-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (1-oxo-3-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [(acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt;
Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester; and
Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester.

4. The use according to Claim 2, wherein the sulfonylaminocarbonyl derivative is sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl-2,6-bis(1-methylethyl)phenyl ester, or a pharmaceutically acceptable salt thereof.

5. The use according to Claim 1, wherein the sulfonylaminocarbonyl derivative is a compound of Formula II



II

or a pharmaceutically acceptable salt thereof wherein:

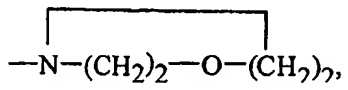
R^1 is hydrogen, alkyl, or alkoxy;
R^2 to R^5 are alkyl, alkoxy, or unsubstituted or substituted phenyl; and
R^6 is -CN,

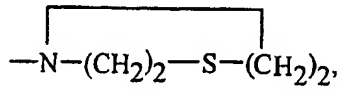
- $(CH_2)_{0-1}$-NR^7R^8,
- O-$(CH_2)_{1-10}$-Z, wherein Z is -NR^9R^{10}, OR^1, or CO_2R^1,
- $OC(=O)R^{11}$,
- SR^{11},
- SCN,
- $S(CH_2)_{1-10}Z$,
- $S(O)_{1-2}R^{12}$, wherein R^{12} is hydroxy, alkoxy, alkyl, $(CH_2)_{1-10}Z$ or NR^7R^8,
- $C(=O)XR^{11}$, or
- CH_2-R^{13}, wherein R^{13} is $(CH_2)_{0-5}$-Y-$(CH_2)_{0-5}Z$, or alkyl of from 1 to 20 carbons with from 1-3 double bonds, which alkyl is optionally substituted by one or more moieties selected from -CN, NO_2, halogen, OR^1, NR^9R^{10}, and CO_2R^1;

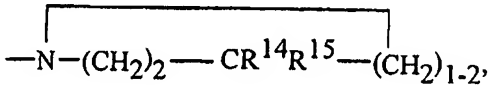
wherein R^7 and R^8 are each independently selected from:

- hydrogen, at least one of R^7 and R^8 is other than hydrogen,
- $(CH_2)_{1-10}Z$, wherein Z is as defined above and R^9 and R^{10} are each independently selected from hydrogen, alkyl, and unsubstituted or substituted phenyl, or

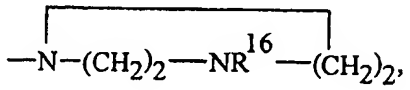
R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a ring selected from:







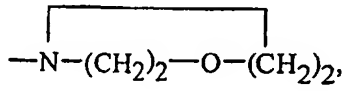
and

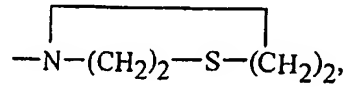


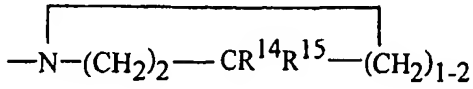
wherein R^{14}, R^{15}, and R^{16} are each independently selected from hydrogen, alkyl, and unsubstituted or substituted phenyl;

- $C(=Q)XR^{11}$, wherein X is a bond or NH wherein Q is O or S, R^{11} is hydrogen, alkyl, unsubstituted or substituted phenyl,
- $(CH_2)_{0-5}$-Y-$(CH_2)_{0-5}Z$, wherein Z is as defined above and Y is phenyl or a bond;
- $C(=O)$-$CR^{17}R^{18}Z$;
- $C(=O)NHCR^{17}R^{18}Z$, wherein R^{17} and R^{18} are each independently hydrogen, alkyl, phenyl, substituted phenyl, or the side chain of a naturally occurring amino acid;
- $S(O)_{1-2}R^{19}$, wherein R^{19} is alkyl, unsubstituted or substituted phenyl, naphthyl, or a heteroaromatic ring, or NR^9R^{10} or

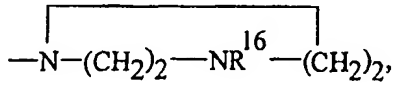
R^7 and R^8 are taken together with the nitrogen to which they are attached to form a ring selected from:







and



wherein R^{14}, R^{15}, and R^{16} are as above, with the proviso that compounds selected from the group consisting of:

[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-formyl-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-cyano-vinyl)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(4-methyl-piperazin-1-ylmethyl)-phenyl ester, dihydrochloride;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[bis-(2-hydroxyethyl)-amino]-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(3-phenyl-thioureido]-phenyl ester; and
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-sulfamoyl-phenyl ester
are excluded.

6. The use according to Claim 5, wherein the sulfonylaminocarbonyl derivative is a compound of Formula II, or a pharmaceutically acceptable salt thereof, selected from:

6-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenyl)-hexanoic acid ethyl ester;
3-[3-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenyl)-ureido]-propionic acid ethyl ester;
{[4-(1-Hydroxy-1-methyl-ethyl)-2,6-diisopropyl-phenyl]-acetyl}-sulfamic acid 2,6-diisopropyl-phenyl ester;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-4-methyl-pentanoylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-tert-butyl-ureido)-2,6-diisopropyl-phenyl ester;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-amino-propionylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-cyanovinyl)-2,6-diisopropyl-phenyl ester;

[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-3-hydroxy-propionylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-4-carbamoyl-butyrylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[2-(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-((S)-2-amino-3-methyl-butyrylamino)-2,6-diisopropyl-phenyl ester; compound with trifluoro-acetic acid;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[3-(3,5-dichloro-phenyl)-thioureido]-2,6-diisopropyl-phenyl ester;
(S)-[5-tert-Butoxycarbonylamino-5-(3,5-diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenylcarbamoyl)-pentyl]-carbamic acid tert-butyl ester;
(S)-[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2,6-diamino-hexanoylamino)-2,6-diisopropyl-phenyl ester dihydrochloride;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-t-butoxycarbonylamino-acetylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-acetylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-t-butoxycarbonylamino-4-methylsulfanyl-butyrylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-4-methylsulfanyl-butyrylamino)-2,6-diisopropyl-phenyl ester trifluoroacetate;
3-[3-(3,5-Diisopropyl-4- { [(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenyl)-ureido]-propionic acid ethyl ester;
3-[3-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl)-acetyl]sulfamoyloxy}-phenyl)-ureido]-propionic acid;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[2-amino-3-(1H-indol-3-yl)-propionylamino]-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(5-amino-pentanoylamino)-2,6-diisopropyl-phenyl ester trifluoroacetate(1:1)(salt);
(D)-[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-propionylamino)-2,6-diisopropyl-phenyl ester trifluoroacetate(1:1)(salt);
(L)-[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-propionylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-amino-2-methyl-propionylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-dimethylamino-propoxy)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-dimethylamino-propoxy)-2,6-diisopropyl-phenyl ester hydrochloride salt;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(3-amino-propoxy)-2,6-diisopropyl-phenyl ester hydrochloride salt;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-thiocyanato-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-cyano-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[(2-amino-acetylamino)-methyl]-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(benzylaminomethyl)-2,6-diisopropyl-phenyl ester mono hydrochloride;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-carbamoyl-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-hydroxymethyl-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-acetylamino-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(2-hydroxyethylamino)-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-[3-(2,6-diisopropyl-phenyl)-ureido]-2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(3-phenyl-ureido]-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-(thiophene-2-sulfonylamino)-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 4-(5-dimethylamino-naphthalene-1-sulfonylamino)- 2,6-diisopropyl-phenyl ester;
[(2,4,6-Triisopropyl-phenyl)-acetyl]-sulfamic acid 2,6-diisopropyl-4-methanesulfonylamino-phenyl ester;
6-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl-acetyl]sulfamoyloxy}-phenyl)-hexanoic acid ethyl ester; and
6-(3,5-Diisopropyl-4-{[(2,4,6-triisopropyl-phenyl-acetyl]sulfamoyloxy}-phenyl)-hexanoic acid.

7. The use according to Claim 1, wherein the sulfonylaminocarbonyl derivative is a compound, or a pharmaceutically

acceptable salt thereof, selected from:

(9H-Xanthene-9-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester;
((E)-2-Methyl-3-phenyl-acryloyl)-sulfamic acid 2,6-diisopropyl-phenyl ester; and
(2-Oxo-2H-chromene-3-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester.

8. The use according to Claim 1, wherein the sulfonylaminocarbonyl derivative is a compound, or a pharmaceutically acceptable salt thereof, selected from:

Carbamic acid, [(phenylamino)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [(phenylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-hydroxyphenyl ester;
Carbamic acid, [(phenylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)phenyl ester;
Carbamic acid, [(didecylamino)sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methylphenyl ester;
Carbamic acid, [[bis(1-methylethyl)amino]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [(dipentylamino)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[(diphenylmethyl)amino]sulfonyl]methyl-, 2,6-bis(1,1-dimethylethyl)phenyl ester;
DL-Tryptophan, α-methyl-N-[[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]sulfonyl]-, methyl ester;
Carbamic acid, sulfonylbis-, bis[2,6-bis(1-methylethyl)phenyl] ester;
Carbamic acid, [[[2-(phenylmethyl)phenyl]amino]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)phenyl ester; Methyl[[2,6-bis(1-methylethyl)phenyl amino]sulfonyl]carbamate; Dodecyl[[2,6-bis(1-methylethyl)phenyl]amino] sulfonyl]carbamate; 2,6-Bis(1,1-dimethylethyl)-4-methoxyphenyl [[(2,2-diphenylethyl)-amino]sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methoxy phenyl [[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)phenyl-[[(diphenylmethyl)amino]-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)phenyl [[[2,6-bis(1-methylethyl)phenyl]-amino]sulfonyl] carbamate;
2,6-Bis(1,1-dimethylethyl)phenyl [[(2,2-diphenylethyl)amino]-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)phenyl [[bis(phenylmethyl)amino]-sulfonyl]carbamate;
2,6-bis(1-methylethyl)phenyl[(diphenyl-amino)sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[(dibutyl-amino)sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[[bis(phenyl-methyl)amino]sulfonyl]-carbamate;
2,6-Bis(1-methylethyl)phenyl[(1H-benzimidazol-2-ylamino)-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl [[2,2-diphenylethyl)amino]sulfonyl]-carbamate;
2,6-Bis(1-methylethyl)phenyl[[[2,6-bis(1-methylethyl)phenyl]-amino]sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[[(diphenyl-methyl)amino]sulfonyl]-carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[(diphenylmethyl)-amino]sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[[bis(2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[(2,2-diphenylethyl)-amino] sulfonyl]-carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[(dibutylamino)-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl [(dipentylamino)-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl [[bis(1-methylethyl)amino]sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl [(dihexylamino)-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl [(hexylamino)-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[methyl(2-phenylethyl)amino]sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[[bis-3-(dimethylamino)propyl]amino]-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[(methyl octyl amino)-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-[[bis[(tetrahydro-2-furanyl)methyl]amino]sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl -phenyl[(dioctylamino)-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[[methyl 2-(2-pyridinyl)ethyl]amino]sulfonyl]carbamate, hydrochloride salt;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[[[methyl 2-(2-pyridinyl)ethyl]amino]-sulfonyl]carbamate, sodium salt;
2,6-Bis(1,1-dimethylethyl)-4-methyl-phenyl[(dodecylamino)-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl [[bis(1 -methylethyl)amino]sulfonyl]-carbamate;
2,6-Bis(1-methylethyl)phenyl[[(1-methylethyl)phenylmethyl)-amino]sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[(hexyl-amino)sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl [(dioctyl-amino)sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[[cyclo-hexyl(1-methylethyl)amino]-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[(methyl-octylamino)sulfonyl]-carbamate;

2,6-Bis(1-methylethyl)phenyl [(dihexyl-amino)sulfonyl]carbamate;
Dodecyl [[(2,4,6-trimethoxyphenyl)amino]-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl ester(4-morpholinylsulfonyl)-carbamic acid;
2,6-Bis(1-methylethyl)phenyl ester(1-piperidinylsulfonyl)carbamic acid;
2,6-Bis(1-methylethyl)phenyl ester(1-pyrrolidinylsulfonyl)-carbamic acid;
2,6-Bis(1-methylethyl)phenyl ester[(2,3-dihydro-1H-indol-1-yl)sulfonyl]carbamic acid;
2,6-Bis(1-methylethyl)phenyl[(dibutylamino)sulfonyl]carbamate monosodium salt; and
2,6-Bis(1,1-dimethylethyl)phenyl[[(diphenylmethyl)amino]-sulfonyl]methyl carbamate .

9. The use according to Claim 1, wherein the sulfonylaminocarbonyl derivative is a compound, or a pharmaceutically acceptable salt thereof, selected from:

Urea, N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dipropylamino)-sulfonyl]-;
Urea, N-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N'-[[(tricyclo[3.3.1.1^{3,7}]dec- 1-ylmethyl)amino]sulfonyl]-, (4S-*cis*)-;
Urea, N-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N'-[[(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)amino]sulfonyl]-, stereoisomer;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis(1-methylethyl)amino]-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(diphenylmethyl)amino]-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(diphenylamino)-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dibutylamino)sulfonyl]urea;
N-[[[2,6-bis(1-methylethyl)phenyl]amino]-sulfonyl]-N'-(diphenylmethyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[[2,6-bis(1-methylethyl)-phenyl]amino]sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(2,2-diphenylethyl)-amino]sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(9H-fluoren-9-ylamino)-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis(phenylmethyl)amino]-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(1-methylethyl)-(phenylmethyl)amino]sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dioctylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(4-phenyl-1-piperidinyl)-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dihexylamino)sulfonyl]-urea;
N-[[bis[3-(dimethylamino)propyl]amino]-sulfonyl]-N'-[2,6-bis(1-methylethyl)phenyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(hexylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis-[(tetrahydro-2-furanyl)methyl]amino]sulfonyl]-urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(diethylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(methyloctyl amino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[cyclohexyl(1-methylethyl)amino] sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dipentylamino)sulfonyl]-urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis(2-methylpropyl)amino]-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[ethyl(2-propenyl)amino]-sulfonyl]urea;
N-[[bis(3-methylbutyl)amino]sulfonyl]-N'-[2,6-bis(1-methylethyl)-phenyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(didecylamino)sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(didodecylamino)-sulfamoyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(diisopropylamino)-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dicyclohexylamino)-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(methyloctadecylamino)-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(di-2-propenylamino)-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[(1,1-dimethylethyl)(1-methylethyl)amino]sulfonyl]-urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[bis(1-methylpropyl)amino]-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(methyltetradecylamino)-sulfonyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-pyrrolidinylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-piperidinylsulfonyl)urea;
N'-[[[2,6-bis(1-methylethyl)phenyl]amino]sulfonyl]-N,N-bis(phenylmethyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[(dibutylamino)sulfonyl]urea, monosodium salt; and
N'-[2,6-bis(1-methylethyl)phenyl]-N-methyl-[(dibutylamino)sulfonyl]urea.

10. The use according to Claim 1, wherein the sulfonylaminocarbonyl derivative is a compound, or a pharmaceutically acceptable salt thereof, selected from:

Sulfamic acid, [[[2,4,6-tris(1-methylethyl)phenyl]amino]-carbonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Sulfamic acid, [[[[1-[4-(dimethylamino)phenyl]cyclopentyl]-methyl]amino]carbonyl], 2,6-bis(1-methylethyl) phenyl ester;
(2,3-Dihydro-indole-1-carbonyl)-sulfamic acid 2,6-diisopropyl-phenyl ester;
Sulfamic acid, [[(triphenylmethyl)amino]carbonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Octadecyl [[[2,6-bis(1-methylethyl)phenyl]-amino]carbonyl]-sulfamate;
Dodecyl-N-[[[2,6-bis(1-methylethyl)phenyl]-amino]carbonyl]-sulfamate;
Decyl [[[2;6-bis(1-methylethyl)phenyl]amino]carbonyl]sulfamate;
(±) 1-Methylheptyl [[[2;6-bis(1-methylethyl)phenyl]amino]-carbonyl]sulfamate;
2;6-Bis(1-methylethyl)phenyl [[[2;6-bis(1-methylethyl)-phenyl]amino]carbonyl]sulfamate;
(±) 1-Methylundecyl [[[2;6-bis(1-methylethyl)phenyl]amino]-carbonyl]sulfamate; and
Dodecyl [[[2;6-bis(1-methylethyl)phenyl]amino]carbonyl]-sulfamate; sodium salt.

11. The use according to Claim 1, wherein the sulfonylaminocarbonyl derivative is a compound, or a pharmaceutically acceptable salt thereof, selected from:

Carbamic acid, [(dodecyloxy)sulfonyl]-, dodecyl ester;
Carbamic acid, [(dodecyloxy)sulfonyl]-,[1,1':3',1"-terphenyl]-2'-yl ester;
Carbamothioic acid, [(dodecyloxy)sulfonyl]-, S-[2,6-bis(1-methylethyl)-phenyl] ester;
Carbamic acid, (phenoxysulfonyl)-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [(2,6-dimethylphenoxy)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1,1-dimethylethyl)phenoxy]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1,1-dimethylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [(2,6-difluorophenoxy)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [(hexadecyloxy)sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-dimethoxyphenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 1-methylheptyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)-4-nitrophenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 1,2-ethanediyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 1,2,3-propanetriyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-bromo-2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, [1,1':3',1"-terphenyl]-2'-yl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1,1-dimethylethyl)-4-methoxyphenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-fluoro-2,3,5,6-tetrakis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-chloro-2,6-bis-(1-methylethyl)phenyl ester;
Stigmasta-5,22-dien-3-ol, [[2,6-bis(1-methylethyl)phenoxy]-sulfonyl]-carbamate, (3α)-;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1,1dimethylethyl)-4-methylphenyl ester;
Stigmastan-3-ol, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-carbamate, (3α)-;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-methoxy-2, 6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4,6-tris(1-methylethyl)phenyl ester;
Carbamic acid, [[2,4,6-tris(1-methylethyl)phenoxy]sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,4,6-tris(1-methylethyl)phenoxy]sulfonyl]-, 2,4,6-tris(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4,6-tris(1,1-dimethylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl] dithio]-2,6-bis(1,1-dimethylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-[(dimethylamino)methyl]-2,6-bis(1-methylethyl) phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-hydroxy-2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, cyclohexyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 3,3',5,5'-tetrakis(1-methylethyl)[1,1'-biphenyl]-4,4'-diyl ester;
Carbamic acid, [[4-hydroxy-2,6-bis(1-methylethyl)phenoxy]-sulfonyl]-, 2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, tricyclo[3.3.1.1^{3,7}]dec-1-yl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2-(1,1-dimethylethyl)-6-methylphenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 5-methyl-2-(1-methylethyl)cyclohexyl ester;

Carbamothioic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, *S*-[2,6-bis(1-methylethyl)phenyl] ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, (2,6-diethylphenyl)methyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, (2*S*,6*S*)-2,6-bis(1-methylethyl)cyclohexyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-(1,1-dimethylethyl)-2, 6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-fluorophenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,4-difluorophenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, pentafluorophenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-difluorophenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, (2*R*,6*S*)-2,6-bis(1-methylethyl)cyclohexyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,3,5,6-tetramethylphenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 3-pyridinyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 2,6-dimethylphenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-acetyl-2,6-bis(1-methylethyl)phenyl ester;
Carbamic acid, [[2,6-bis(1-methylethyl)phenoxy]sulfonyl]-, 4-fluoro-2,6-bis(1-methylethyl)phenyl ester;
2,6-Bis(1-methylethyl)phenyl[[2,6-bis(1-methylethyl)phenoxy]-sulfonyl]carbamate;
2,6-Bis(1;l -dimethylethyl)-4-methylphenyl (phenoxysulfonyl)-carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methylphenyl [(hexyloxy)-sulfonyl]carbamate;
2,6-Bis(1,1-dimethylethyl)-4-methylphenyl[(dodecyloxysulfonyl]carbamate;
Dodecyl[[2,6-bis(1-methylethyl)phenoxy]-sulfonyl]carbamate;
Methyl[[2,6-bis(1-methylethyl)phenoxy]-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl[(hexyloxy)-sulfonyl]carbamate;
2,6-Bis(1-methylethyl)phenyl](dodecyloxy)-sulfonyl]carbamate; and
2,6-Bis(1,1-dimethylethyl)phenyl[[2,6-bis(1-methylethyl)-phenoxy]sulfonyl]carbamate .

12. The use according to Claim 1, wherein the sulfonylaminocarbonyl derivative is a compound, or a pharmaceutically acceptable salt thereof, selected from:

N-[2,6-bis(1-methylethyl)phenyl]-N'-(6-ethoxy-2-benzothiazolyl)-sulfonyl]-urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-octadecylsulfonyl)urea;
N-[2,4,6-trimethoxyphenyl]-N'-(2-octadecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(tetradecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(dodecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(hexadecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-methyl-N'-(dodecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(tridecylsulfonyl)urea;
N-[2,4,6-trimethoxyphenyl]-N'-(hexadecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-methyl-2-pentadecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-phenyl-1-tetradecylsulfonyl)urea;
N-2,6-bis(1-methylethyl)phenyl-N'-(dodecylsulfonyl)urea;
N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-phenyl-1-nonylsulfonyl)urea; and
N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-decylsulfonyl)urea.

13. The use of Claim 1, wherein the disease or disorder being treated is rheumatoid arthritis, osteoarthritis, an autoimmune disease, psoriasis, asthma, a cardiovascular disease, an acute coronary syndrome, congestive heart failure, Alzheimer's disease, multiple sclerosis, cancer, type II diabetes, metabolic syndrome X, or inflammatory bowel disease.

14. The use according to Claim 13, wherein the disease or disorder being treated is selected from the group consisting of: systemic lupus erythematosus, Grave's disease, myasthenia gravis, insulin resistance, autoimmune hemolytic anemia, scleroderma with anticollagen antibodies, pernicious anemia, and diabetes mellitus.

15. The use according to Claim 13, wherein the disease or disorder being treated is rheumatoid arthritis .

16. The use according to Claim 13, wherein the disease or disorder being treated is osteoarthritis.

17. The use according to Claim 13, wherein the disease or disorder being treated is insulin resistance.

18. The use according to Claim 13, wherein the disease or disorder being treated is asthma.

19. The use according to Claim 13, wherein the disease or disorder being treated is atherosclerosis.

20. The use according to Claim 13, wherein the disease or disorder being treated is myocardial infarction ·

21. The use according to Claim 13, wherein the disease or disorder being treated is unstable angina.

22. The use according to Claim 13, wherein the disease or disorder being treated is congestive heart failure.

23. The use according to Claim 13, wherein the disease or disorder being treated is Alzheimer's disease,

24. The use according to Claim 13, wherein the disease or disorder being treated is cancer.

25. The use according to Claim 13, wherein the disease or disorder being treated is inflammatory bowel disease.

26. The use according to Claim 13, wherein the disease or disorder being treated is multiple sclerosis.

27. The use according to Claim 13, wherein the disease or disorder being treated is psoriasis.

28. The method according to Claim 13, wherein the disease or disorder being treated is type II diabetes.

29. The method according to Claim 13,wherein the disease or disorder being treated is metabolic syndrome X.

30. Use of a sulfonylaminocarbonyl derivative or a pharmaceutically acceptable salt thereof for preparing a pharmaceutical composition for inhibiting NF-κB transcription factors in an animal.

31. A pharmaceutical composition, comprising a nuclear factor-κB transcription factor inhibiting amount of a sulfonylaminocarbonyl derivative, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 02 00 2612

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,X	US 5 254 715 A (PICARD JOSEPH A ET AL) 19 October 1993 (1993-10-19) * the whole document * ---	1,2,8, 13,19, 20,30,31	A61K31/18 A61K31/255 A61K31/27
D,X	US 5 336 690 A (PICARD JOSEPH A ET AL) 9 August 1994 (1994-08-09) * the whole document * ---	1,2,8, 13,19, 20,30,31	
D,X	US 5 214 206 A (SLISKOVIC DRAGO R ET AL) 25 May 1993 (1993-05-25) * the whole document * ---	1,2,9, 13,19, 20,30,31	
D,X	US 5 288 757 A (PICARD JOSEPH A ET AL) 22 February 1994 (1994-02-22) * the whole document * ---	1,2,9, 13,19, 20,30,31	
D,X	US 5 198 466 A (SLISKOVIC DRAGO R ET AL) 30 March 1993 (1993-03-30) * the whole document * --- -/--	1,2,10, 13,19, 20,30,31	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K
A61P

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	27 June 2002	Skjöldebrand, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

INCOMPLETE SEARCH SHEET C

Application Number
EP 02 00 2612

Claim(s) searched completely:
3-30

Claim(s) searched incompletely:
1,2

Reason for the limitation of the search:

The definition of the therapeutical indication in claim 1, "a disorder responsive to inhibition of NF-kB transcription factors" does not clearly delimit what diseases fall under the scope of the claim. The search has therefore been performed for the disorders listed in claims 13-29.

Moreover, a "sulfaminocarbonyl derivative" relate to an extremely large number of possible compounds . Support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC is to be found, however, for only a very small proportion of the compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Claim 2 is not clear, because there is no substituent R in the generic formula 1. Instead, there is an oxygen-atom attached to the nitrogen, which is inconsitent with the claims depending on claim 2. It is therefore assumed that the R is connected as in generic formula 1 on description page 5.
Nitrogen is not incliuded in the definition of X and Y, although some compounds in the claims dependent on claim 2 do contain nitrogen in these positions.

A search of the general formula in claim 2 (corrected, as defined on description page 5) in conjunction with keywords related to the diseases (claims 13-29) revealed such a large number of documents that, for economical reasons, it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 84 EPC). For these reasons, a meaningful search over the whole breadth also of claim 2 is impossible.

Consequently, the search has been restricted to:
The compounds listed in claims 3-12 and the diseases as in claims 13-29.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 00 2612

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
D,X	US 5 364 882 A (PICARD JOSEPH A ET AL) 15 November 1994 (1994-11-15) * the whole document *	1,2,10, 13,19, 20,30,31	
D,X	US 5 245 068 A (PICARD JOSEPH A ET AL) 14 September 1993 (1993-09-14) * the whole document *	1,2,11, 13,19, 20,30,31	
D,X	US 5 384 328 A (PICARD JOSEPH A ET AL) 24 January 1995 (1995-01-24) * the whole document *	1,2,11, 13,19, 20,30,31	
X	US 6 117 909 A (KRAUSE BRIAN ROBERT) 12 September 2000 (2000-09-12) * the whole document *	1-4,13, 19,20, 30,31	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
D,X	US 5 491 172 A (LEE HELEN T ET AL) 13 February 1996 (1996-02-13) * the whole document *	1-6,13, 19,20, 30,31	
D,X	US 6 093 744 A (LEE HELEN TSENWHEI ET AL) 25 July 2000 (2000-07-25) * the whole document *	1-6,13, 19,20, 30,31	
D,X	US 5 633 287 A (LEE HELEN T ET AL) 27 May 1997 (1997-05-27) * the whole document *	1-7,13, 19,20, 30,31	

-/--

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 00 2612

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	WO 97 44314 A (WARNER LAMBERT CO ;LEE HELEN TSENWHEI (US); PICARD JOSEPH ARMAND () 27 November 1997 (1997-11-27) * the whole document * ---	1-6,13, 19,20, 30,31	
D,X	US 5 254 589 A (PICARD JOSEPH A ET AL) 19 October 1993 (1993-10-19) * the whole document * ---	1,2,12, 13,19, 20,30,31	
D,X	US 5 981 595 A (PICARD JOSEPH ARMAND ET AL) 9 November 1999 (1999-11-09) * the whole document * ---	1,2,12, 13,19, 20,30,31	
D,X	US 6 124 309 A (BOCAN THOMAS M A) 26 September 2000 (2000-09-26) * the whole document * ---	1,2,13, 19,20, 30,31	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	WO 98 32733 A (PFIZER ;DOMBROSKI MARK ANTHONY (US); EGGLER JAMES FREDERICK (US)) 30 July 1998 (1998-07-30) * abstract; claims * ---	1,2, 12-14, 19,20, 23,26, 30,31	
X	DESFAITS A C ET AL: "Gliclazide reduces the induction of human monocyte adhesion to endothelial cells by glycated albumin." DIABETES, OBESITY & METABOLISM. ENGLAND MAR 1999, vol. 1, no. 2, March 1999 (1999-03), pages 113-120, XP001080461 ISSN: 1462-8902 * abstract * --- -/--	1,13-31	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 02 00 2612

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	BOCAN T M A ET AL: "THE ACAT INHIBITOR AVASIMIBE REDUCES MACROPHAGES AND MATRIX METALLOPROTEINASE EXPRESSION IN ATHEROSCLEROTIC LESIONS OF HYPERCHOLESTEROLEMIC RABBITS" ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, XX, XX, vol. 20, no. 1, January 2000 (2000-01), pages 70-79, XP000997385 ISSN: 1079-5642 * abstract * ---	1-4,19, 20,30,31	
P,X	WO 01 21159 A (NOVARTIS ERFIND VERWALT GMBH ;PONGOWSKI MICHELE (CH); NOVARTIS AG) 29 March 2001 (2001-03-29) * abstract * ---	1,14,28, 30,31	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
P,X	EP 1 145 717 A (PFIZER PROD INC) 17 October 2001 (2001-10-17) * abstract; claims * ---	1,13,14, 17,28-31	
X	US 5 948 886 A (BURKHART JOSEPH P ET AL) 7 September 1999 (1999-09-07) * abstract * ---	1,13,15, 25,30,31	
X	PICARD J A ET AL: "Inhibitors of acyl-CoA:cholesterol O-acyltransferase. 17. Structure-activity relationships of several series of compounds derived from N-chlorosulfonyl isocyanate." JOURNAL OF MEDICINAL CHEMISTRY. UNITED STATES 15 MAR 1996, vol. 39, no. 6, 15 March 1996 (1996-03-15), pages 1243-1252, XP001080050 ISSN: 0022-2623 * abstract; tables * ---	1-13,19, 20,30,31	
	-/--		

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 00 2612

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	ROTH B D ET AL: "Inhibitors of acyl-CoA: cholesterol acyltransferase (ACAT). 15. sulfonylurea inhibitors with excellent hypocholesterolemic activity in vivo" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 5, no. 20, 19 October 1995 (1995-10-19), pages 2367-2370, XP004135266 ISSN: 0960-894X * abstract; tables * ---	1,12,13, 19-22, 30,31	
X	US 3 983 249 A (ZITOWITZ LESTER ET AL) 28 September 1976 (1976-09-28) * abstract * -----	1,13,21, 30,31	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03.82 (P04C10)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 00 2612

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-06-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5254715 A	19-10-1993	AU 651155 B2	14-07-1994
		AU 8950991 A	11-06-1992
		CA 2094807 A1	08-05-1992
		EP 0592439 A1	20-04-1994
		IE 913875 A1	20-05-1992
		JP 6501706 T	24-02-1994
		JP 2000319179 A	21-11-2000
		MX 9101957 A1	08-07-1992
		NZ 240480 A	26-08-1994
		PT 99436 A ,B	30-09-1992
		US 5336690 A	09-08-1994
		WO 9208693 A1	29-05-1992
		ZA 9108810 A	06-05-1993
US 5336690 A	09-08-1994	US 5254715 A	19-10-1993
		AU 651155 B2	14-07-1994
		AU 8950991 A	11-06-1992
		CA 2094807 A1	08-05-1992
		EP 0592439 A1	20-04-1994
		IE 913875 A1	20-05-1992
		JP 6501706 T	24-02-1994
		JP 2000319179 A	21-11-2000
		MX 9101957 A1	08-07-1992
		NZ 240480 A	26-08-1994
		PT 99436 A ,B	30-09-1992
		WO 9208693 A1	29-05-1992
		ZA 9108810 A	06-05-1993
US 5214206 A	25-05-1993	AT 139226 T	15-06-1996
		AU 657928 B2	30-03-1995
		AU 8959791 A	11-06-1992
		CA 2094806 A1	08-05-1992
		DE 69120287 D1	18-07-1996
		DE 69120287 T2	10-10-1996
		DK 556322 T3	14-10-1996
		EP 0556322 A1	25-08-1993
		ES 2088128 T3	01-08-1996
		GR 3020355 T3	30-09-1996
		IE 913874 A1	20-05-1992
		JP 3256541 B2	12-02-2002
		JP 6501707 T	24-02-1994
		JP 2001026574 A	30-01-2001
		MX 9101958 A1	08-07-1992
		NZ 240481 A	27-06-1994
		PH 30665 A	16-09-1997
		PT 99435 A ,B	31-12-1992

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 00 2612

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-06-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5214206 A		US 5288757 A	22-02-1994
		WO 9208694 A1	29-05-1992
		ZA 9108809 A	06-05-1993
US 5288757 A	22-02-1994	US 5214206 A	25-05-1993
		AT 139226 T	15-06-1996
		AU 657928 B2	30-03-1995
		AU 8959791 A	11-06-1992
		CA 2094806 A1	08-05-1992
		DE 69120287 D1	18-07-1996
		DE 69120287 T2	10-10-1996
		DK 556322 T3	14-10-1996
		EP 0556322 A1	25-08-1993
		ES 2088128 T3	01-08-1996
		GR 3020355 T3	30-09-1996
		IE 913874 A1	20-05-1992
		JP 3256541 B2	12-02-2002
		JP 6501707 T	24-02-1994
		JP 2001026574 A	30-01-2001
		MX 9101958 A1	08-07-1992
		NZ 240481 A	27-06-1994
		PH 30665 A	16-09-1997
		PT 99435 A ,B	31-12-1992
		WO 9208694 A1	29-05-1992
		ZA 9108809 A	06-05-1993
US 5198466 A	30-03-1993	AT 117986 T	15-02-1995
		AU 652207 B2	18-08-1994
		AU 9070191 A	11-06-1992
		CA 2094808 A1	10-05-1992
		DE 69107217 D1	16-03-1995
		DE 69107217 T2	24-05-1995
		DK 556308 T3	26-06-1995
		EP 0556308 A1	25-08-1993
		ES 2070623 T3	01-06-1995
		GR 3015648 T3	31-07-1995
		IE 913911 A1	20-05-1992
		JP 3177245 B2	18-06-2001
		JP 6501486 T	17-02-1994
		MX 9101986 A1	01-06-1992
		NZ 240509 A	26-07-1994
		PT 99465 A ,B	30-10-1992
		WO 9208692 A1	29-05-1992
		US 5364882 A	15-11-1994
		ZA 9108888 A	10-05-1993

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 00 2612

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-06-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5364882 A	15-11-1994	US 5198466 A	30-03-1993
		AT 117986 T	15-02-1995
		AU 652207 B2	18-08-1994
		AU 9070191 A	11-06-1992
		CA 2094808 A1	10-05-1992
		DE 69107217 D1	16-03-1995
		DE 69107217 T2	24-05-1995
		DK 556308 T3	26-06-1995
		EP 0556308 A1	25-08-1993
		ES 2070623 T3	01-06-1995
		GR 3015648 T3	31-07-1995
		IE 913911 A1	20-05-1992
		JP 3177245 B2	18-06-2001
		JP 6501486 T	17-02-1994
		MX 9101986 A1	01-06-1992
		NZ 240509 A	26-07-1994
		PT 99465 A ,B	30-10-1992
		WO 9208692 A1	29-05-1992
		ZA 9108888 A	10-05-1993
US 5245068 A	14-09-1993	US 5384328 A	24-01-1995
		AT 116291 T	15-01-1995
		AU 654688 B2	17-11-1994
		AU 8937091 A	26-05-1992
		CA 2093510 A1	01-05-1992
		DE 69106386 D1	09-02-1995
		DE 69106386 T2	04-05-1995
		DK 555351 T3	06-06-1995
		EP 0555351 A1	18-08-1993
		ES 2067254 T3	16-03-1995
		FI 931838 A	23-04-1993
		GR 3014992 T3	31-05-1995
		IE 913774 A1	22-05-1992
		JP 6502415 T	17-03-1994
		NO 179445 B	01-07-1996
		NZ 240404 A	25-02-1994
		PT 99360 A ,B	30-09-1992
		WO 9207826 A1	14-05-1992
		ZA 9108606 A	29-04-1993
US 5384328 A	24-01-1995	US 5245068 A	14-09-1993
		AT 116291 T	15-01-1995
		AU 654688 B2	17-11-1994
		AU 8937091 A	26-05-1992
		CA 2093510 A1	01-05-1992
		DE 69106386 D1	09-02-1995

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 00 2612

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-06-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5384328 A		DE 69106386 T2	04-05-1995
		DK 555351 T3	06-06-1995
		EP 0555351 A1	18-08-1993
		ES 2067254 T3	16-03-1995
		FI 931838 A	23-04-1993
		GR 3014992 T3	31-05-1995
		IE 913774 A1	22-05-1992
		JP 6502415 T	17-03-1994
		NO 179445 B	01-07-1996
		NZ 240404 A	25-02-1994
		PT 99360 A ,B	30-09-1992
		WO 9207826 A1	14-05-1992
		ZA 9108606 A	29-04-1993
US 6117909 A	12-09-2000	AU 716255 B2	24-02-2000
		AU 6454196 A	05-03-1997
		BG 102222 A	30-09-1998
		CA 2221729 A1	20-02-1997
		CN 1192140 A	02-09-1998
		CZ 9800261 A3	15-07-1998
		EA 980176 A1	29-10-1998
		EE 9800037 A	17-08-1998
		EP 0841913 A1	20-05-1998
		HR 960341 A1	28-02-1998
		HU 9900668 A2	28-06-1999
		JP 11510184 T	07-09-1999
		NO 980466 A	03-02-1998
		NZ 312571 A	28-07-2000
		PL 324908 A1	22-06-1998
		SK 12598 A3	11-02-1999
		WO 9705868 A1	20-02-1997
US 5491172 A	13-02-1996	AT 178891 T	15-04-1999
		AU 681152 B2	21-08-1997
		AU 6831194 A	12-12-1994
		CA 2158268 A1	24-11-1994
		CZ 9502966 A3	11-09-1996
		DE 69417885 D1	20-05-1999
		DE 69417885 T2	30-09-1999
		DK 698010 T3	25-10-1999
		EP 0698010 A1	28-02-1996
		ES 2133163 T3	01-09-1999
		FI 955438 A	10-11-1995
		GR 3030356 T3	30-09-1999
		HU 72653 A2	28-05-1996
		JP 8510256 T	29-10-1996

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 00 2612

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-06-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5491172 A		NO 954564 A	11-01-1996
		NZ 266689 A	24-11-1997
		RU 2137756 C1	20-09-1999
		SG 47056 A1	20-03-1998
		SK 139695 A3	06-11-1996
		WO 9426702 A1	24-11-1994
		US 5633287 A	27-05-1997
		ZA 9403313 A	13-11-1995
US 6093744 A	25-07-2000	AU 2738897 A	09-12-1997
US 5633287 A	27-05-1997	US 5491172 A	13-02-1996
		AT 178891 T	15-04-1999
		AU 681152 B2	21-08-1997
		AU 6831194 A	12-12-1994
		CA 2158268 A1	24-11-1994
		CZ 9502966 A3	11-09-1996
		DE 69417885 D1	20-05-1999
		DE 69417885 T2	30-09-1999
		DK 698010 T3	25-10-1999
		EP 0698010 A1	28-02-1996
		ES 2133163 T3	01-09-1999
		FI 955438 A	10-11-1995
		GR 3030356 T3	30-09-1999
		HU 72653 A2	28-05-1996
		JP 8510256 T	29-10-1996
		NO 954564 A	11-01-1996
		NZ 266689 A	24-11-1997
		RU 2137756 C1	20-09-1999
		SG 47056 A1	20-03-1998
		SK 139695 A3	06-11-1996
		WO 9426702 A1	24-11-1994
		ZA 9403313 A	13-11-1995
WO 9744314 A	27-11-1997	AU 2738897 A	09-12-1997
		WO 9744314 A1	27-11-1997
		ZA 9704231 A	11-12-1997
US 5254589 A	19-10-1993	AU 2869792 A	21-05-1993
		MX 9205893 A1	01-04-1993
		PT 100960 A	30-11-1993
		US 5981595 A	09-11-1999
		WO 9308161 A1	29-04-1993
US 5981595 A	09-11-1999	US 5254589 A	19-10-1993
		AU 2869792 A	21-05-1993

EPC FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 00 2612

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-06-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5981595 A		MX 9205893 A1	01-04-1993
		PT 100960 A	30-11-1993
		WO 9308161 A1	29-04-1993
US 6124309 A	26-09-2000	AU 720853 B2	15-06-2000
		AU 7253996 A	22-05-1997
		BG 102417 A	29-01-1999
		BR 9611410 A	05-01-1999
		CA 2233558 A1	09-05-1997
		CN 1201389 A	09-12-1998
		CZ 9801271 A3	16-12-1998
		EA 980420 A1	29-10-1998
		EP 0858336 A1	19-08-1998
		HU 9901865 A2	28-10-1999
		JP 11515025 T	21-12-1999
		NO 981961 A	04-05-1998
		NZ 319906 A	28-02-2000
		PL 326365 A1	14-09-1998
		SK 55798 A3	11-06-1999
		WO 9716184 A1	09-05-1997
		US 6093719 A	25-07-2000
		US 6143755 A	07-11-2000
		ZA 9609187 A	29-05-1997
WO 9832733 A	30-07-1998	AP 929 A	18-01-2001
		AU 723895 B2	07-09-2000
		AU 5234098 A	18-08-1998
		BG 103597 A	29-02-2000
		BR 9714328 A	21-03-2000
		CN 1245490 A	23-02-2000
		EP 0964849 A1	22-12-1999
		HR 980045 A1	30-06-1999
		HU 0000567 A2	28-10-2000
		WO 9832733 A1	30-07-1998
		JP 2000511200 T	29-08-2000
		NO 993658 A	28-09-1999
		NZ 336248 A	27-10-2000
		PL 335052 A1	27-03-2000
		SK 98299 A3	08-10-2001
		TR 9901816 T2	22-11-1999
		US 6166064 A	26-12-2000
		ZA 9800685 A	29-07-1999
WO 0121159 A	29-03-2001	AU 7904400 A	24-04-2001
		BR 0014525 A	11-06-2002
		CZ 20011723 A3	15-08-2001

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 00 2612

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-06-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0121159 A		WO 0121159 A2	29-03-2001
		EP 1212077 A2	12-06-2002
		FI 20010683 A	02-04-2001
		FR 2798592 A1	23-03-2001
		NO 20021197 A	16-05-2002
		IT MI20002019 A1	15-03-2002
EP 1145717 A	17-10-2001	BR 0101461 A	13-11-2001
		EP 1145717 A2	17-10-2001
		JP 2001354568 A	25-12-2001
		US 2002013268 A1	31-01-2002
US 5948886 A	07-09-1999	US 6172044 B1	09-01-2001
US 3983249 A	28-09-1976	DE 2415064 A1	10-10-1974
		FR 2223017 A1	25-10-1974
		GB 1449404 A	15-09-1976
		JP 50029730 A	25-03-1975

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82